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NUTRITION AND THE WAR*

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IT IS a distinct honor to be invited to give the Shattuck Lecture, with its long list of distinguished former lecturers and its tradition of excellence of the addresses. I therefore appreciate greatly this honor that has come to me and the opportunity to address the Massachusetts Medical Society on this occasion.

So far as the practice of medicine is concerned, the title of my lecture is somewhat of a misnomer, because the direct contribution of the war to clinical nutrition was not very great. Actual nutritional-deficiency disease was not common in the troops. Most of the actual work in nutrition was in the field of preventive medicine and was not concerned with nutritional disease in the individual patient. Even among prisoners of war and civilian populations, study and observation added little to our knowledge of the severer forms of these diseases. There were, as we shall see, examples of some unusual manifestations of deficiencies. The absence of certain anticipated deficiencies was noteworthy. In Europe particularly the preponderance of calorie and protein deficiency and the rarity of vitamin deficiencies in the civilian populations were striking. But aside from these observations little that is new was obtained from direct observation. The war did, however, intensify interest and speed up research in nutrition. As a result so much has been done that the end of hostilities provides a useful point at which to pause, survey what has been done and consider the place of some of this new knowledge of nutrition in the practice of medicine.

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There are many aspects of nutrition, but those with which the physician is primarily interested are the prevention of nutritional-deficiency disease and its diagnosis and treatment. Ordinarily the physician's interest in the general prevention of nutritional-deficiency disease is rather academic unless he happens to be a public-health officer. The private practitioner does have, however, a very real personal interest in this aspect of nutrition, and if he is alert he will maintain a general acquaintance in this field. It is from the general population that his patients are drawn, and the background of nutrition of that population may influence very considerably the nature of the illnesses of his patients, their reaction to disease and their response to his treatment. To some extent this interest, indeed this self-interest, has been appreciated by pediatricians and by a few other physicians, but in general it has not received the attention it deserves. In contrast to general prevention, the prevention of nutritional-deficiency disease in individual patients is of much greater immediate importance to the practicing physician — a problem with which he must deal every day and in some degree or other with almost every patient.

Existing nutritional-deficiency disease is encountered by the doctor in two forms. One is an idiopathic or primary disease caused by a dietary inadequacy, often the result of socioeconomic factors over which the patient may or may not have some control. The other is a conditioned disease in which the deficiency is dependent on some other illness that causes a nutritional deficiency or permits it to develop. The illnesses or abnormalities that cause or induce the deficiency are of the most varied kinds, ranging from severe organic gastrointestinal disease to mild psychoneurosis. This is the kind of nutritional deficiency disease that will be encountered oftenest by the practicing physician and is of the greatest immediate importance to him. It is also the kind that he should be most alert and active to prevent, the more so because such deficiency disease may be the direct result of things he does or fails to do, things directly subject to his control. Often they are relatively simple things, and often failure to control them has a very significant effect on the patient.

There are certain differences between the idiopathic and conditioned type of disease in relation to prevention and treatment. Idiopathic deficiencies ordinarily exist before the patient goes to the doctor. Either they are the disease for which the

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patient seeks relief, or they are a substratum to which is added whatever other disease the patient may acquire. Conditioned deficiency diseases, on the other hand, are developed subsequent to some other illness. Although often present by the time the doctor first sees the patient, in many cases, especially those associated with acute illness and trauma, they do not occur until after the conditioning disease begins. This gives the doctor opportunity to prevent or minimize them. In conditioned deficiency, then, the opportunity for prevention is greater. In the idiopathic disease, diagnosis and treatment of an existing deficiency is the problem.

At the present time the principal nutritional-deficiency diseases that can be diagnosed and are considered to be of clinical significance in man are caused by a lack of the necessary amounts of the following substances: calories, protein, vitamin A, thiamin, niacin, riboflavin, folic acid (*L. casei* factor), ascorbic acid or vitamin C, vitamin K, iron and calcium. There are others, notably those of water and sodium chloride, and perhaps some of the other electrolytes, that we can recognize clinically. Some would add vitamin E, certain of the so-called "trace elements" and perhaps others of the vitamin B complex. But these are not yet well enough established, if indeed they exist, as recognizable clinical disease to warrant inclusion here.

From these I have selected for discussion those that at present seem to be of considerable importance to clinical medicine, or about which there is new and interesting knowledge. However, before proceeding with that discussion I wish to clarify the use and meaning of certain terms. The term "nutritional deficiency" has two meanings depending on whether one is referring to a deficiency in the dietary, or the intake of food, or whether one is referring to the state of nutrition of the body. In health the body possesses a reserve of nutrients. Therefore, it is possible for a dietary nutritional deficiency to exist without a state of nutritional deficiency in the body. Only when a pathologic change in structure or function has occurred can we speak of nutritional-deficiency disease. Clear understanding and attention to this relation will prevent much confusion and misunderstanding.

* * *

Two nutritional factors that have assumed a new and important place in clinical medicine during the war are the energy principle (calories) and protein. In 1897, just about fifty years ago, Dr. Frederick C. Shattuck[1] wrote a paper, "Diet in Typhoid Fever," in which he advocated the use of relatively large amounts of food in this disease. Although he lacked a knowledge of all the underlying biochemical processes that demand such treatment, his practice was sound and represents for most practical purposes the recently developed concepts of nutrition in relation to injury and disease.

Simple, idiopathic calorie-and-protein-deficiency disease is not ordinarily seen by physicians. On the contrary, conditioned deficiency of these factors is one of the most frequent, perhaps the most frequent, of all the nutritional deficiencies seen in practice. Yet far too little attention has been paid to them despite the existence for many years of the example of typhoid fever. Here, a severe infectious disease, with a long, debilitating course, a relatively high mortality and a prolonged convalescence, was converted into a much less severe, less fatal illness during which patients often gained weight, maintained good general condition and recovered more quickly, by the simple provision of an adequate calorie diet. Why the medical profession, with this experience before its eyes, has been willing to accept the severe weight losses and debility accompanying other infectious diseases and illnesses as a natural and inescapable concomitant of those diseases is rather incomprehensible.

Although it is customary to distinguish between calorie and protein deficiency, I should like to present the thesis that, so far as disease is concerned, there is only a deficiency of protein and that for all practical purposes starvation, aside from lack of vitamins and minerals, is protein starvation. Under ordinary circumstances a healthy person possesses some slight reserve of carbohydrate (glycogen) and a considerable reserve of fat, amounting roughly to 10 per cent of the body weight, sometimes much more. When there is a dietary deficiency of calories this reserve is drawn on and used for energy (calories). Only when the fat is all or nearly all gone does the draft on tissue protein begin, and only when this exceeds a certain as yet indefinite point does actual nutritional deficiency disease begin. Under some conditions, as we shall see, there may be a direct loss of tissue protein without reference to calorie levels. When, however, calories are inadequate this loss is increased.

Recent studies, especially those conducted during the war, have provided much new knowledge about this deficiency and emphasized its importance as a frequent and serious complication of a variety of diseases, ranging from certain kinds of trauma and injury to infections and infectious diseases. The circumstances and nature of the deficiency are as follows. Many kinds of injury and disease are accompanied by a negative nitrogen balance. This means that more nitrogen is excreted than is taken into the body in the form of protein. Even so simple a restriction as confinement in bed may produce this effect. The most striking and uncomplicated examples are seen in fractures of the large bones in previously healthy and well nourished persons. Under these circumstances the negative nitrogen balance stands out as a sharply defined abnormality clearly related to the acute injury and without any background of other disease or apparent cause. Accompanying the negative nitrogen balance there

is usually a negative calorie balance, which increases the deficiency of nitrogen (protein).

This phenomenon persists for a variable length of time and exists to a variable degree, depending on factors to be discussed later. If it is severe enough and of long enough duration, the body reserves of protein are exhausted and actual protein deficiency disease develops as I have described. This is responsible for the loss of weight, muscle atrophy, weakness and other effects of such an illness.

This phase, which is often spoken of as the catabolic phase of the reaction to injury or disease, may last for weeks, and is succeeded by an anabolic phase, during which the nitrogen balance becomes positive, nitrogen is retained and protein formed, tissues are restored, and weight is regained. It corresponds to the period of convalescence and recovery.

Besides fractures, this abnormality occurs in a wide variety of other injury and disease — in severe burns, after major surgical operations, especially those in which the peritoneum is opened, with infections such as osteomyelitis and abscesses and with some infectious diseases, such as typhoid fever and meningitis. The cause of this metabolic and nutritional disturbance is not clearly known. There is some evidence that it is linked to the adrenal glands and perhaps to other endocrines. It is a positive, independent reaction not related solely to deficient intake, although intensified by the latter as we shall see. Usually the negative balance continues despite an increase in nitrogen intake, excretion increasing with intake, and in some cases, despite exceedingly large intakes of protein, this negative nitrogen balance cannot be overcome. Because of this and because of its essential nature it has been thought by some to represent a beneficial or protective reaction to injury and disease that should not be overcome.

This specific or essential negative nitrogen balance is exaggerated by a number of other factors that are very important in producing the clinical state of deficiency disease. Following the injury, or with the onset of the disease, there is usually a loss of appetite and a resultant decrease in the intake of food and hence of calories and protein. To this specific loss of appetite there are often added the factors of unappetizing meals, poorly prepared and served, weakness, difficulties brought about by recumbency or by complicated apparatus, nausea and vomiting and the mental changes of illness, all of which interfere with the intake of food. Unfortunately to these must often be added indifference on the part of the doctor and nurse to problems of nutrition, and even misconception and ignorance regarding proper diet and nutrient requirements. The importance of those factors is shown by the results of a survey of food consumption in Canadian military hospitals.[2] This revealed such disparities as a decrease in a diet from about 4000 calories and 156 gm. of protein as planned to 2600 calories and 75 gm. of protein as actually served, with a further reduction to 1850 calories and 54 gm. of protein actually eaten. Similar studies in one of our own military hospitals revealed high-carbohydrate, low-fat diets for convalescents containing as little as 1400 to 1600 calories and actual intakes as low as 800 calories.[3]

Besides these deficiencies of intake there are other secondary factors affecting nitrogen loss of even greater importance. Although in the primary reaction the nitrogen is lost mainly by urinary excretion, there is often a large added loss in exudates, drainage from wounds and from the surface of burns and even in the sputum and gastric contents and, in those cases with albuminuria, an added loss through the kidneys. Often these losses are tremendous. Thus the specific and primary defect is greatly exaggerated and the nutritional deficiency increased. In diseases not associated with this specific metabolic disorder a nitrogen and protein loss can, of course, occur as the result of simply a dietary deficiency, leading to the same protein-deficiency disease.

The effect of this negative calorie and protein balance depends on its severity and duration and on the nutritional state of the patient. If it is mild and of short duration in a well nourished person, little harm is done. The body has sufficient reserves of protein and body fat to tide him over. To say that in such cases nutritional deficiency disease exists would be incorrect. What has occurred is a metabolic disturbance or abnormality. However, if the reaction is severer and more prolonged, or if it occurs in patients with inadequate reserve of these nutrients, actual deficiency disease does occur. Curiously, if the patient is already much undernourished, the primary, specific negative nitrogen balance does not occur or is of slight degree, as though the body were incapable of responding to an injury or disease in the normal manner. However, reflection will show that under these circumstances the body is already in a state comparable to that reached in the latter stages of the catabolic phase of the reaction, and that nutritional disease already exists.

In addition to the initial reaction, similar, though usually less severe, reactions may occur as the result of complications during the course of the illness. Thus the changing of casts, secondary operations, the opening of abscesses and the occurrence of a secondary or complicating infection or infectious disease may all be accompanied by a return or exaggeration of the nitrogen deficit and of the nutritional-deficiency disease.

The outward manifestation of this deficiency disease is a loss of body weight. At first slight and representing mostly loss of fat, when more severe and continued there is loss of tissue protein, revealed externally by atrophy of muscles. There is, however, also a loss of native protein, from important parenchymatous organs and from the blood plasma.

These changes have recently been carefully studied experimentally by Keys and his associates.[4] Keys's subjects had only simple protein deficiency, but the effects so far as loss of protein from the tissues and organs is concerned are basically similar to those seen accompanying injury and disease with a primary negative nitrogen balance. In Keys's experiment previously healthy men were given about half the calories they expended daily, a regime designed to reduce their weight by about 25 per cent in a few months. In these subjects, in addition to the severe loss of weight, muscle atrophy, weakness and mental changes, there occurred edema, great atrophy of such viscera as the heart and physiologic changes, such as severe hypothermia, bradycardia and lowered basal metabolism.

In patients with injury or disease many of these abnormalities are even severer. Others are masked or modified, and not necessarily in a favorable way, by various factors not present in simple starvation. For instance, fever and infection prevent bradycardia and maintain or elevate the basal metabolism. The weakened heart may be enlarged instead of smaller. Edema is often greater and more dependent on hypoproteinemia. In Keys's cases the edema failed to show a close relation to plasma protein levels, and it is probable that other factors were concerned in its production, the likeliest one in my opinion being loss of tissue pressure resulting from the rapid and severe loss of weight. In patients, on the other hand, the nutritional edema is usually associated with a hypoproteinemia, often severe.

These, then, are the changes and the cause of the changes that produce much of the picture of serious illness so well known to physicians. They increase mortality, increase morbidity, predispose to complications, prolong the course of illness and delay convalescence and recovery. If they can be prevented or relieved, the course of disease becomes shorter and less severe, complications fewer, and the outcome more favorable. Reference has already been made to the possibility that the negative nitrogen balance occurring in injury and disease constitutes a protective and favorable reaction, and that therefore it may be inadvisable to suppress or abolish it. This is possibly true, and the difficulty or even impossibility of overcoming the negative balance early in the catabolic phase, nitrogen being excreted as fast as it is taken in, supports such a concept. Nevertheless there are many examples of reactions to disease, primarily beneficial, that when excessive become harmful and retard recovery. It seems improbable that protein losses to the point of severe weakness, muscle atrophy and hypoproteinemia can be beneficial, and experience suggests that measures to relieve, if not completely abolish, this reaction shorten it, hasten and strengthen the phase of recovery and prevent or minimize the untoward effects of this reaction. Much attention is being paid at the present time to early ambulation, but early ambulation is useless, or even harmful or impossible, unless a proper state of nutrition is maintained or secured.

From this discussion it is apparent that in practice there are two stages of this reaction that can be rather sharply differentiated and that differ in their practical management. The first is the initial period when only the metabolic disturbance is present and no nutritional-deficiency disease has occurred. When the patient is seen in this stage there is the possibility of preventing or minimizing serious effects. The second is the stage when a greater or lesser deficiency has developed. In many cases this condition has developed under the eyes of the physician, and either it is ignored or the more difficult process of treatment rather than prevention is attempted.

As for the practical management of this problem and the maintenance or restoration of the proper nutritional state, I fear I must promise you Churchill's prospect of "blood, sweat and tears." Most of you, if you make an honest attempt to secure the benefits of such a regime, will sweat blood and weep tears. The principle is simple and easy. No difficult, highly specialized or expensive technics or materials are necessary. But perhaps because of this, and because it does require close attention and supervision on the part of the physician and the nursing and other staffs, as well as the wholehearted co-operation of the patient, in the drab day-by-day business of getting food into the patient, it is a difficult problem. That it *can* be solved is shown by the success in the modern treatment of typhoid fever.

Much help can be derived from the use of standardized procedures or "routines," particularly in a hospital. However, as always, each patient will present an individual problem, his requirements will differ as will his response, and he will need individual attention. Routines can provide only the basic framework of the procedure, within which adjustments must be made for each patient.

A patient when seen by the physician should have an appraisal of the state of nutrition, the probable effects of the disease on his nutrition and what is needed for the prevention or treatment of nutritional disease. Often this will require only the usual history, physical examination and routine laboratory work, but special laboratory tests may be needed. For the patient who is injured or develops an illness in a normal state of nutrition, the need can be determined in general from the nature of the illness and its severity and probable duration, but complications and variations in the response of the patient and his co-operation may require modification from time to time. For instance, in fractures of the large bones, or severe trauma, in serious burns and in most major surgical operations for acute diseases, an immediate negative nitrogen balance

and calorie deficit can be anticipated. This should be met by nitrogen and calorie intakes to overcome or minimize these deficiencies. Standardized regimes are useful, but mainly to indicate the amount and kind of food and route of administration. *They will not assure its consumption.* Varco[5] has recently published a number of excellent diets for this purpose in a variety of surgical conditions. In general, 3000 to 5000 calories and 120 to 150 gm. of protein are necessary and advisable. As has already been said, experience has shown that in many cases it is not necessary or desirable to secure complete nitrogen equilibrium during the early and more marked stage of the catabolic reaction, the disadvantages and untoward results of attempting to supply huge amounts of protein outweighing the advantages. However, sufficient protein and calories should be administered to provide a high intake of nitrogen, overcome the calorie deficit and take full advantage of the beginning of the anabolic period, which will probably be hastened by this treatment.

When possible, this nourishment should be provided as ordinary food, supplemented when necessary by special feedings. Such supplemental feedings will be required in most cases. In general an attempt should be made to secure an intake of around 2500 calories and 90 to 100 gm. of protein by ordinary meals. The need for care in preparation and serving of the food and for assistance to the patient in eating is very great, and on this depends much of the success of the procedure. Fortunately, after an adequate or satisfactory intake has been secured for a few days the appetite generally improves and many patients will voluntarily consume large quantities of food.

The additional requirements are met by supplements. These are most satisfactorily furnished as milk drinks, composed of milk with added skim-milk powder, or prepared casein, and glucose. A variety of satisfactory formulas have been devised. A typical one provides 28 gm. of protein and 343 calories for each 240 cc. Therefore, three such feedings will add 84 gm. of protein and 1029 calories a day, bringing the daily intake to over 3500 calories and 160–180 gm. of protein if the regular meals are consumed. Special recipes for other high-protein foods developed by the Medical Dietetic Division of the Army's Medical Nutrition Laboratory[6] are helpful in securing a high intake of protein.

The simplest guide in the management of these patients is loss of weight, which, except for the complication of edema, is quite a sensitive index of the state of protein nutrition. In general, it may be assumed that losses of more than 10 per cent below the ideal calculated weight are evidence of actual protein deficiency. However, in obese persons protein loss may occur before calorie deficiency and weight loss are apparent. Many patients are, of course, over their ideal weight and can tolerate larger losses of their actual weight so far as fat is concerned. The metabolism of large amounts of fat, however, increases considerably the work of the liver, and in some circumstances, especially those in which there may be injury to the liver, this may not be desirable. This is particularly true in view of the recent evidence of the greater susceptibility of the liver to injury in conditions of protein deficiency.

Accurate nitrogen-balance studies are not often needed in these patients. A careful record of intake — calories and nitrogen — should be maintained in such patients, and it can be assumed that if intakes of around 3500 to 4000 calories and 120 to 150 gm. of protein are secured the nitrogen deficit will be abolished or minimized in most cases. Losses beyond about 10 per cent of calculated ideal body weight should be avoided, and if losses exceed this figure a more careful determination of the nitrogen balance should be made. In burned patients, particularly, and in those with exudates, draining sinuses, dysentery and other causes of abnormal loss of protein, a careful check of the probable balance must be made to determine the necessary intake, which in some cases may be unusually large. For instance, it has been calculated that an average-sized man with a third-degree burn of 50 per cent of his body surface may lose as much as 199 gm. of nitrogen in twenty-four hours from the burned surface, equivalent to 124 gm. of protein. To replace this loss requires 600 gm. of meat, or about 2000 cc. of plasma, and the amount estimated to be necessary to put some patients in nitrogen equilibrium has been calculated to be as much as 2000 gm. of meat, or 23 units of plasma.[7]

Particular attention must be paid to edema because of its nutritional significance and because it masks an actual loss of tissue. Retention of 10 pounds of water can occur without visible edema. Except in patients with complicating renal or cardiac disease, the edema is nearly always related to hypoproteinemia, which can be detected by determining the concentration of the plasma proteins. Ordinarily the determination of the total serum proteins by the simple specific-gravity methods suffices as a general guide, but the greater significance of the albumin and the possibility that albumin is depressed while total protein remains normal or near normal make it necessary to determine serum-protein fractions when such a condition is suspected.

With patients who are already in a state of nutritional-deficiency disease, more strenuous treatment is necessary because the problem is one of replacement rather than prevention — the replacement of losses rather than maintenance of reserves. Furthermore, speed is highly desirable, and delay merely prolongs recovery and convalescence. Weight, with due consideration for edema, is again the best general evidence of the state of protein nutrition and the loss of protein from the tissues.

Muscular atrophy supports this finding. Hypoproteinemia indicates the cause of edema, and its degree is a rough index of the degree of protein loss and atrophy of the other body tissues and organs as well as of the plasma. Intakes as high as 5000 to 6000 calories or higher and 200 to 300 gm. of protein may be required and very effective, although often somewhat smaller amounts suffice.

In patients with nutritional disease already established and in some other circumstances, the ordinary intake of food by mouth proves inadequate and parenteral feeding may be necessary. It may also be necessary in delirious or mentally ill patients, in those with disease of the gastrointestional tract, especially as a preoperative procedure when haste is necessary or desirable, and for those who do not co-operate by ingesting adequate amounts of food. Ordinarily, parenteral feeding is best accomplished by stomach or duodenal tube, which can be used intermittently or for a continuous drip. For this purpose a variety of formulas for liquid foods are available, most of them similar to those used for supplemental feeding by mouth. There is, however, one valuable and notable addition — solutions of amino acids. These preparations, although very unpleasant when taken by mouth, are well tolerated if given by gastric or duodenal tube, are very efficient in replacing protein and make it possible to introduce large amounts of nitrogen with relative ease. Only solutions known to be satisfactory and capable of maintaining nitrogen balance when constituting the only source of nitrogen should be used.

In some cases it may be necessary to use intravenous feeding, alone or in combination with gastric or duodenal gavage. Ordinarily such intravenous feeding is only for replacement of nutrients lost acutely, such as in operations or trauma, and includes red blood cells, plasma, fluid and electrolytes. It is assumed in this discussion that such replacement of acute losses has been made. Occasionally, however, intravenous feeding is necessary for the maintenance or restoration of nutrition. For this purpose plasma or a solution of amino acids is used for nitrogen, and glucose for fuel. Nitrogen and calorie balance can be maintained by these means. However, except for replacement of acute losses, plasma is relatively ineffective. In existing states of protein deficiency and in many cases of burns and other diseases with large protein losses, the requirements are so great that it is physically impossible to satisfy them with plasma. Solutions of amino acids meet this objection and provide a fairly satisfactory means of restoring and maintaining nutrition over relatively long periods. There are numerous drawbacks to intravenous feeding, however. One is the amount of fluid necessary, which may overtax a weak heart, cause circulatory failure, induce or exaggerate edema and even provoke pulmonary edema and secondary pneumonia. Thrombosis of the veins used for injection occurs and may interfere with prolonged feeding. The psychologic influence of eating is lacking. Therefore intravenous feeding, particularly by itself, should be used only after careful consideration of the need and suitability, and for no longer than necessary.

Nothing has been said of vitamins and minerals, which are ordinarily less important to these patients than calories and protein. They will be discussed elsewhere. Except perhaps in burned patients they present little difficulty in previously healthy individuals. Adequate amounts for maintenance should be assured, and if these amounts are not available in the food they should be provided as supplements. In particular, provision should be made for adequate amounts of those vitamins directly concerned with cellular oxidations — thiamin, riboflavin and niacin — when patients are maintained on large intakes of pure carbohydrates, such as glucose, that carry with them no complementary vitamins. When given parenterally somewhat larger doses of these vitamins should be given than normally required because of greater excretion. In previously ill patients, or those seen for the first time with nutritional-deficiency disease, an appraisal should be made of their status in respect to vitamins and minerals and adequate restorative and maintenance treatment should be instituted.

Before leaving the subject of protein nutrition I should like to speak briefly of another condition that has a close similarity to injury and disease so far as liability to protein deficiency is concerned. I refer to pregnancy. The basis for the similarity is as follows. During pregnancy there is normally a positive nitrogen balance occasioned by the need of protein for the products of conception, and probably some for storage against the demands of lactation. If this requirement is not met by the food, the needed amount is taken from the mother's tissues. Thus there occurs a condition similar to the negative nitrogen balance of disease and injury, and if it is anything but minimal and if it continues for anything but a few days there will occur, just as in fractures, burns or typhoid fever, actual protein-deficiency disease. Also, as in fractures and burns, secondary factors may complicate and exaggerate the deficiency in pregnancy. Vagaries of appetite, nausea and vomiting, misinformed restriction of diet and such factors may all have such an effect.

Following delivery there is a negative nitrogen balance. In part this is due to involution, the excess nitrogen coming from the genital organs and tissues. But there may be still another loss, that of lactation. It has been estimated that during lactation 2 gm. of nitrogen is needed every day for every gram of nitrogen in the milk if nitrogen equilibrium is to be maintained.[8] Loss of blood during delivery constitutes an additional nitrogen loss. Unless sufficient protein is taken in to replace these losses, the protein must come from the maternal tissues. In those

women who have failed to establish an adequate reserve during pregnancy, or who have even suffered from an actual protein deficiency, this additional protein loss may be a serious drain.

Recent studies indicate a close relation between nutrition, particularly protein nutrition, and the toxemias of pregnancy. For example, Tompkins[9] found four times as many toxemias of pregnancy in a group of women with dietaries limited in protein as in those on a diet containing 110 gm. of protein daily; five times as many with edema; and eight times as many with pre-eclampsia. In 1400 pregnant women Holmes[10] found twice as many with toxemias of pregnancy in those with protein intakes of 60 to 70 gm. as among those with intakes of 110 to 120 gm. Edema is much oftener due to protein deficiency and hypoproteinemia than to renal or cardiac disease, and some cases of the anemia of pregnancy may have the same cause. Thus, the greater need for protein during pregnancy and the harmful effects of an actual protein deficiency require that protein be furnished in larger amounts at this time. Intakes of at least 1.5 gm. per kilogram of body weight should be provided, and somewhat larger amounts are probably desirable. During lactation the intake should equal 2 gm. per kilogram.

Two other aspects of protein nutrition of clinical importance in both primary and conditioned deficiency disease received attention during the war. One is the relation of protein to the formation of immune bodies. These substances, which are of vital importance in resistance to infectious disease, are contained in the gamma-globulin fraction of the serum proteins and are elaborated by the globulin-producing cells of the liver and reticuloendothelial tissue. In their formation protein is required, and moreover protein containing the essential amino acids. When the amount of such protein in the diet is inadequate, it can be derived for a time from the body tissues. But, when actual protein deficiency occurs and atrophy of the tissues ensues, production of the immune bodies becomes inadequate. Even the production and activity of the phagocytes is impaired, and this second defense against infection is weakened.[11]

The other aspect of protein nutrition is the action of the specific amino acids. Since some ten of the amino acids cannot be synthesized by the body and must be obtained in the food or some other exogenous source, it is obvious that deficiencies of these nutrients must occur. As yet, however, there is no known recognizable clinical expression of such deficiencies. We do know, however, that unless these amino acids are present in adequate amounts it is impossible to maintain nitrogen equilibrium, and there is a loss of nitrogen from the body that probably represents the breakdown of some body protein to supply the amino acid for a more essential purpose. Thus there occurs again a loss of protein from the tissues, which, if great enough and long enough continued, must result in protein deficiency. Therefore it is necessary, in applying protein to prevent or relieve protein deficiencies, to provide protein containing adequate amounts of the essential amino acids.

It is also known that certain amino acids, notably methionine, are utilized in certain processes in the liver concerned with detoxification and that an adequate supply of protein containing such amino acids probably protects the liver against injury in certain endogenous and exogenous intoxications, such as anesthesia,[12] as well as against the effect of certain diseases, such as infectious hepatitis. This protective action fails or is inadequate in cases of protein deficiency.

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Turning now to the vitamins, deficiencies of vitamin A are often neglected in medical practice because of the rarity of xerophthalmia, outspoken night blindness or a severe dermatosis. Perhaps the erroneous concept of vitamin A as the anti-infective vitamin has given it a bad name among doctors. Vitamin A is not per se anti-infective. However, vitamin A deficiency is fairly frequent. Although in a recent review it is stated that it is probably infrequent in this country,[13] a report from Holland in the following issue of the same journal refers to it as the only vitamin deficiency that was observed in a great number of children.[14] It is the only vitamin deficiency, aside from rickets, commonly seen in Germany and Austria at the present time and has been rather prominent in France, Spain and other European countries. Although the signs and symptoms of the deficiency are not specific, they are suggestive and can be supported by determination of vitamin A concentration in the blood. Distinctly low values for the latter, in the absence of temporary causes, can be considered indicative of vitamin A deficiency from a practical clinical point of view.

Vitamin A is particularly important in pregnancy. The child is dependent on the mother for its supply, and the drop in blood vitamin A seen in the latter months of pregnancy[15] may represent in part the transfer from mother to child. If the mother's supply is low, she may deplete her own store and yet fail to furnish the infant with a sufficient store. When breast fed, the child is dependent on the mother's milk for an increase in its store of vitamin A, which is normally less than that of adults, gradually increasing as the child grows. An inadequate endowment may fail to be improved or even maintained if the child receives an inadequate postpartum supply from its mother, a serious deficiency because vitamin A is important in the growth of children. Fortunately, the widespread use of fish-oil supplements in this country, mainly to prevent rickets, tends to prevent greater deficiency of vitamin A among our children, an important reason for

the use of fish oil concentrates rather than preparations of vitamin D alone at this period of life.

Vitamin A deficiency is to be expected in diseases leading to faulty digestion, particularly of fats. It is found also in jaundiced states, because lack of bile hinders absorption, and in various forms of parenchymatous disease of the liver, in which the deficiency may be due to a failure to convert carotene to vitamin A or to store the latter. Recently vitamin A has become of interest in clinical medicine in another way. Vitamin A-tolerance tests, — similar to the glucose-tolerance test, — especially when combined with similar determinations of blood carotene, are useful in the diagnosis of sprue, celiac disease and diseases of the liver of various kinds. The blood levels of carotene and vitamin A are particularly useful in the differential diagnosis of sprue and pernicious anemia, the carotene being low in sprue and normal in pernicious anemia, with vitamin A usually low in sprue and normal in pernicious anemia. Ruffin and Wise[16] have recommended the vitamin A-tolerance test to distinguish between various kinds of hepatitis and obstructive jaundice, tolerance being low in the former and normal in the latter. A high concentration of plasma carotene with a low concentration of vitamin A suggests a failure of liver function. Of even greater interest are preliminary observations of Darby and his associates[17] at Vanderbilt, which suggest that vitamin A tolerance may be a more sensitive indication of recovery of liver functions in infectious hepatitis than such tests as cephalin flocculation.

A deficiency of ascorbic acid is one of the more frequent vitamin deficiencies seen in medical practice, although actual scurvy is uncommon. However, to wait for the appearance of scurvy before considering the possibility and significance of this deficiency is unwise. The pathologic changes of scurvy are progressive, their extent and severity depending on the degree and duration of the deficiency. Before the classic changes of scurvy are observed, less severe but nevertheless harmful lesions must have developed. It is true that scurvy, or even minor deficiency signs, may not appear in subjects experimentally kept on virtually zero intakes for months. This situation, however, is different from that of the patient who for many months or for years has failed to consume adequate amounts and who may have had an inadequate absorption or utilization or a destruction of the vitamin. Because of the frequency of conditioning or predisposing factors in medical practice, doctors should not be misled by misinterpreting data from studies on normal subjects.

Among the most recent findings in regard to vitamin C metabolism, a result of research during the war, are observations such as those of Andrae and Browne,[18] who found a high ascorbic acid retention in patients with thermal burns and fractures. This they believed could not be attributed to pre-existing deficiency, faulty absorption or impaired excretion, retention in the tissues or edema fluid, or excretion in the form of dehydroascorbic acid. Although the exact significance of these observations is not clear, the large doses of the vitamin retained during the first week of such illnesses suggest the desirability of treatment with large doses of vitamin C in these cases.

Among the vitamin B complex factors, the frequency of thiamin deficiency has, in my opinion, been greatly overestimated and the use of thiamin in practice has been grossly excessive. To begin with, the human requirements for thiamin have been shown to be less than was previously believed. The "recommended allowances" of the National Research Council's Food and Nutrition Board have recently been reduced, and there is good evidence that amounts even considerably less are not accompanied by any recognizable alteration in either nutritional status or physical and psychomotor performance. A source of confusion and error concerning the frequency of thiamin deficiency is mistaken diagnosis in patients said to have beriberi, especially of the wet type, in whom the distal tendon reflexes and the vibratory and other sensory functions are perfectly preserved, and in whom there are no localized muscle weakness and no muscle atrophy. This error has been increased by the erroneous belief that requirements for thiamin are increased in certain environments, such as that of the tropics, and in part by increased excretion in the sweat, neither of which is true. It is interesting that with all the dietary deficiencies that have accompanied the war and involved large populations, thiamin deficiency, except in certain regions in the Pacific and the Far East, has been conspicuous by its rarity. The explanation is found in the long extraction of bread grains that goes with food shortages and the frequent use of various legumes to eke out the supply of flour. The more frequent occurrences in the Pacific seem to be due to the persistence of the custom of using polished rice even when the supply of rice is inadequate. In the Chinese troops I examined, the absence of beriberi was always associated with the use of unhulled rice.

Nevertheless, deficiencies of thiamin do occur, and it must be remembered that slight dietary deficits long continued will eventually deplete the reserves, leaving the person dependent on current intake, which may be sharply reduced by various conditioning factors. Keys and his associates[19] have shown that, although human subjects can be maintained in good condition for weeks on amounts in the neighborhood of 0.22 mg. per 1000 calories, a sudden drastic reduction below that level is quickly followed by serious manifestations of deficiency.

One of the newer clinical observations during the war was the finding of a rather large number of cases of severe optic neuritis and, apparently, of neuritis of the eighth nerve caused by thiamin deficiency.

These lesions are, however, apparently encountered only in severe and long-continued deficiency. In ordinary practice they are seen rarely, usually in alcoholic patients.

Although the signs of early or mild thiamin deficiency are not particularly reliable, a near-zero urinary excretion or an extremely poor response to a test dose of the vitamin can for ordinary clinical purposes be considered as indicative of at least a depleted and vulnerable state of thiamin nutrition. In the more acute and severe deficiencies that may suddenly supervene in chronic mild deficiencies, the pyruvic acid concentration in the blood may add helpful evidence if complicating factors of exercise or other disease are eliminated. Diagnosis of a deficiency of thiamin should not ordinarily be made if there is a good urinary excretion of the vitamin.

An important development in respect to riboflavin has been the accumulating evidence of the nonspecificity of some of the manifestations attributed to a deficiency of this vitamin. The latest has been the demonstration by Darby[20] that perlèche and the glossitis attributed to riboflavin deficiency may respond dramatically, at least in some cases, to the administration of iron, the state of iron deficiency being established by demonstrating a large absorption of radioactive iron (Fig. 1).

Undoubtedly the most important recent development in relation to niacin (nicotinic acid) and pellagra has been the finding of Elvehjem and his associates of the relation of niacin metabolism to the amino acid tryptophane. In their original report these authors[21] showed that the niacin requirements of rats are apparently greatly increased by the feeding of large amounts of corn. Subsequent studies have shown that the effect is due to the low tryptophane content of the diet, and that the addition of tryptophane increases the bacterial synthesis of niacin in the intestine and enables the animal to grow despite a low dietary intake of niacin.[22] Changes in the carbohydrate of the diet have a somewhat similar effect, dextrin favoring the synthesis of niacin, and sucrose lessening it. Although these studies were confined to rats and their significance for man is not fully established, they are cited because they indicate the possibly important role of intestinal bacterial synthesis of vitamins in human nutrition.

The newest vitamin shown definitely to be related to disease in man is a member of the vitamin B complex, the so-called "*L. casei* factor" or folic acid. Previous studies with animals had shown it to be related to diarrhea and anemia in monkeys, under the designation vitamin M,[23] and later to anemia, leukopenia and agranulocytopenia in rats.[24] The material was synthesized in 1945.[25] Later in the same year, Spies and his associates[26] reported that it caused a reticulocytosis, with increased red cells and hemoglobin, in certain human cases of macrocytic anemia that were not well defined by the authors. At about the same time Darby, Jones and Johnson[27] reported that in patients with sprue there was a prompt relief of glossitis and stomatitis, cessation of diarrhea, a sharp reticulocytosis followed by an increase of red cells and hemoglobin, great gain in weight and strength, a return to normal of the glucose and vitamin A tolerance and a lessening of fat in the stools following the injection of 15 mg. daily. Examination of the bone marrow showed a striking return to normal, with greatly increased

FIGURE 1. *Photograph of a Patient with Glossitis and Perlèche (Angular Stomatitis).*

This woman of forty-five, who had a hemoglobin level of 6.5 gm., was relieved by adequate doses of iron following demonstration of iron deficiency by measured absorption of radioactive iron.

maturation of the red cells. These findings have been amply confirmed. The material has been shown to be effective by mouth, and smaller, though definite, responses have been obtained with much smaller doses. In addition, it has been shown to be effective in anemias of the Addisonian type. Recently Darby and Jones[28] have observed a patient with pernicious anemia in relapse who responded with a reticulocytosis of some 25 per cent six days after receiving 3 mg. of the vitamin daily by mouth (Fig. 2). This is the more remarkable because the degree of anemia in this patient was not such as to suggest a response of that magnitude from the use of the usual liver extract.

So far the exact relation of this vitamin to the antipernicious principle of liver, to the extrinsic factor of Castle and to other aspects of pernicious anemia is not clear. It is apparent, however, that

we have in this vitamin a powerful agent for the relief and prevention of serious macrocytic anemias, sprue and possibly some disorders of the leukocytes.

* * *

Anemia related to folic acid deficiency is not the only anemia caused by nutritional deficiencies. A frequent nutritional anemia is iron-deficiency anemia. This is, in fact, one of the commonest nutritional diseases seen by doctors in this country, despite the fact that it is found principally in children and women.

Iron-deficiency anemia is almost always a conditioned deficiency in adults, and in them is rarely due to a dietary deficiency of iron alone. The body conserves iron so carefully that almost none is lost except by hemorrhage and, in females, by transfer to the fetus. Children require iron for growth in addition to the endowment they receive from their mothers at birth. From this it is apparent that iron-deficiency anemia occurs under the following circumstances: failure of a normal endowment, intakes inadequate to meet the demands of growth, and hemorrhage. Actually the first two of these mechanisms are often combined. The mother furnishes from her own store, and at its expense, iron for the hemoglobin of the fetus. But with inadequate stores of her own she may fail to endow the infant with sufficient reserve. Growth requires additional amounts, and with an inadequate dietary intake may fail to meet demands. In adults, loss of blood from any one of a great variety of causes — chronic bleeding hemorrhoids, metrorrhagia, peptic ulcer, frequent pregnancies (complicated by a contribution to the fetus) and surgical operations — may reduce the reserve to a point that makes it impossible to restore normal levels of hemoglobin.

From a dietary and nutritional point of view it is important to note that an anemia of this type will not respond to dietary iron alone. Pharmaceutical preparations of iron must be given in adequate doses.

These are the reasons why iron-deficiency anemia is so particularly a responsibility of the doctor. Its development is almost entirely due to conditions with which he is directly concerned; its cure requires his services. All this is known to most of us, but the surprising thing is the number of people at the present time with this disease, sufficient to interfere with their health and efficiency, in whom it is not recognized and not treated. Patients with a history of loss of blood are operated on; they lose more blood; they receive one or more transfusions and are finally discharged convalescent with the hemoglobin returning to normal. But it does not reach normal, and a surprising amount of ill-health continues. The proof of the cause of the ill-health is the demonstration of an uptake of iron characteristic of iron deficiency, a response of the blood to adequate doses of iron and a relief of symptoms. Clinically this is shown by a significant reticulocytosis.

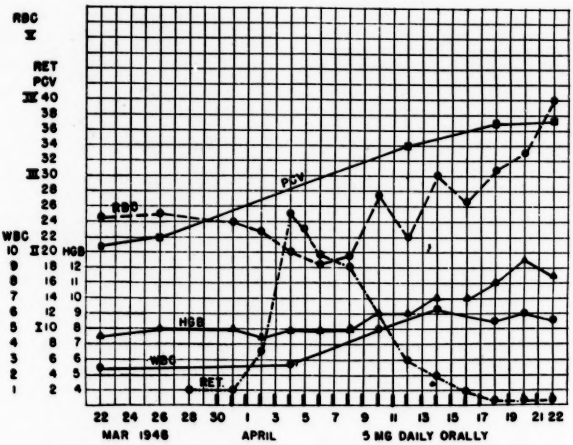

FIGURE 2. *Response to Orally Administered Folic Acid.*
This chart shows the reticulocytosis and response of red cells and hemoglobin to a daily dose of 5 mg. of synthetic L. casei *factor (folic acid) by mouth in a woman of sixty-three.*

This concludes my discussion of some of the phases of nutrition that concern medical practice. If I have dwelt overlong on protein nutrition, it is because I believe that it is the major problem of nutrition in clinical medicine today. On the successful prevention and treatment of this nutritional deficiency disease depend a tremendous improvement in medical care, a great decrease in mortality and morbidity from injury and trauma and from disease and illness of many kinds and great advances in the management of pregnancy, and in child health and development. Other nutrients and nutritional deficiencies are important, and their control will contribute to the improvement in health. By careful individual attention to nutritional requirements and to the prevention or cure of nutritional deficiencies, their ill effects, both primary and on the course of other injury and disease, may be prevented. It is not, however, a thing that can be accomplished without effort. Only if the physician devotes as much attention, relatively, to this as he does to other phases of the care of the sick and injured can he hope to gain for himself and his patients the benefits that our modern knowledge of nutrition has to offer.

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THE USE OF THE SOUTH AFRICAN FROG (*XENOPUS LAEVIS*) IN THE DIAGNOSIS OF PREGNANCY*

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THE use of the South African clawed frog (*Xenopus laevis*) in a test for pregnancy was first reported some years ago,[1, 2] only five years after Aschheim and Zondek's original description of the mouse test in 1929.

Like its predecessors, the test is based on the stimulation of the ovaries by the gonadotropic hormones excreted in the urine of pregnant women or of persons harboring neoplastic chorionic tissue. eight hours and usually within twenty-four hours. The clinical importance of this relative speed is obvious in diagnostic problems, such as in threatened rupture of tubal pregnancy and in certain other surgical conditions. Since the frog reacts to a positive test by the extrusion of hundreds of eggs, the simplicity of reading the test is apparent (Figs. 1 and 2), obviating the necessity, as in the rabbit, rat or mouse tests, of surgery or sacrifice of the

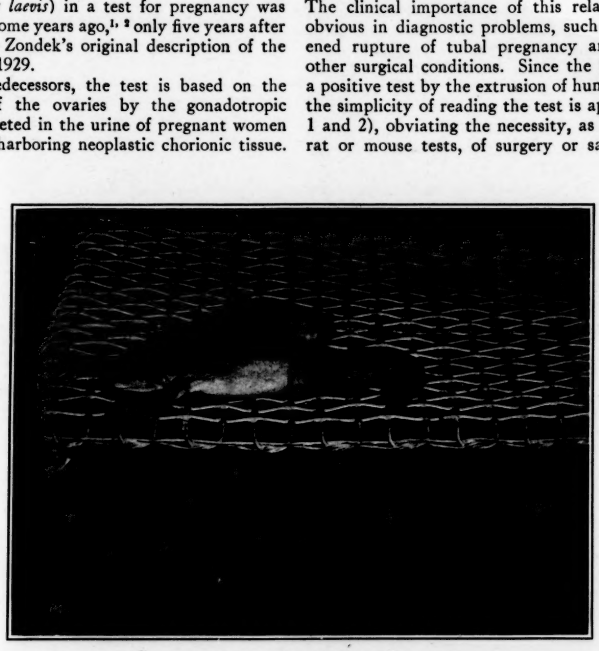

Figure 1. *Negative Frog Test.*

The adult South African clawed frog is peculiarly suited for this procedure because its ovaries always contain eggs, which the frog never extrudes unless it is contacted by the male or unless the ovaries are artificially stimulated by gonadotropic hormones. The frog test has many significant practical and economic advantages over the Aschheim–Zondek and Friedman tests. Whereas the rabbit, rat and mouse tests require two to five days for their performance, the frog test can be read often within animals to visualize the ovarian changes. In addition, the histologic technics employed in other tests are completely unnecessary in this procedure. The frogs can be used over and over again with thirty days' rest after a positive test and with five days' rest after a negative test. Since these animals cost $6 apiece and have an active reproductive life of ten to twelve years, the cost of performing each test is rendered appreciably lower than that of other methods in which the use of experimental animals is limited to a single observation or at best to three or four observations. All these factors, together with the ease in maintaining and feeding the frogs, make them wholly satisfactory diagnostic animals for pregnancy tests.

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The accuracy of the clawed-frog test, in comparison with that of the older, more widely accepted technics, is perhaps the most important factor. During the past year, over 100 urine specimens have been tested by this method at the Mallory Institute of Pathology. In every case the urine used was one of the routine specimens received daily at the laboratory. It is the purpose of this paper, in addition to emphasizing the many advantages of the clawed-frog method, to report on its reliability in the routine diagnosis of pregnancy.

Technic

As was previously mentioned, the technic for the performance of the test is extremely simple. Eighty cubic centimeters of the first morning urine is required for concentration.[3] To this amount is added double the volume of acetone, and the precipitate is spun down in a centrifuge. The supernatant is discarded, and the sediment is washed once or twice with ether by resuspension and centrifugation. After being dried, the material is dissolved in 2 cc. of normal physiologic saline solution, the reaction is adjusted to pH 5.5, and 1 cc. of this concentrate is injected into the dorsal lymph sac of each of two frogs. This method concentrates the hormones present in 40 cc. of urine into a volume of 1 cc. In most cases, a positive test, denoted by the extrusion of eggs, can be read within eight to twelve hours. A negative result, however, should not be assumed until at least twenty-four hours has elapsed. It is worth mentioning that cases with suspected low hormone titers, such as may be encountered in very early pregnancy, incomplete abortion or a blighted ovum, can frequently be detected by the concentration of larger volumes of urine (160 cc.), the same procedure as outlined above being used and the final sediment being dissolved in the same volume of saline solution.

Results

For the sake of comparison, the 100 cases in this series have been divided into four groups — those of possible normal pregnancy, those of suspected ectopic pregnancy, those in which the patient was in the process of miscarrying and the problem of the viability of the gestation hinged on the hormone level in the urine and those of obvious intra-abdominal tumor in which the possibility of concomitant pregnancy was entertained. In every case parallel control injections of urine were made into immature rats, following the procedure outlined by Aschheim and Zondek.

In the few cases in which the frog and the rat methods failed to agree, the clinical record of the patient was consulted. Where necessary, through the co-operation of the clinical services, repeated physical examinations and hormone analyses were made until no further doubt about the final diagnosis existed.

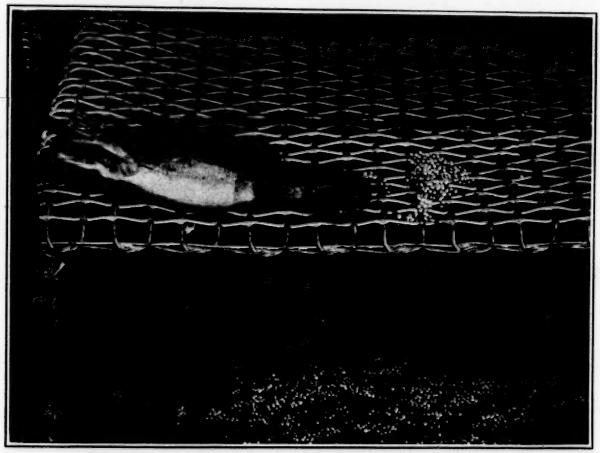

Figure 2. *Positive Frog Test.*
Note the numerous eggs on the screen and the floor of the tank.

The results of the frog test are analyzed in Table 1 from the standpoint of correct or incorrect diagnosis. As the table indicates, in 4 cases the frog test gave false-negative results. In the 2 cases of miscarriage in which the reaction was negative, the clinical courses of the patients were practically identical and in both cases the urine sample had been obtained within hours of the actual passage of the fetus, as the following case indicates.

D. McD., a 35-year-old woman, entered the hospital on May 11, 1945, because of the onset of irregular vaginal bleeding, with the passage of clots but no tissue or fetus. The last menstrual period had occurred on January 5. In March there was an episode of slight vaginal staining, which lasted for 2 days. In an effort to determine whether the fetus was still viable, a urine sample was taken on the day of admission. Several hours later the patient passed the fetus. When the urine was tested, the Aschheim–Zondek test was positive, and the frog reaction was negative.

In the 2 cases of ectopic pregnancy in which the frog test gave a false-negative result, the duration of the pregnancies at the time the urine specimens were obtained was less than six weeks. The clinical history of the more interesting case is as follows:

L. C., a 32-year-old housewife, entered the hospital on June 8, 1945, because of the onset of lower abdominal pain of 2 days' duration, accompanied by vaginal bleeding. The last menstrual period, which had occurred at the normal time on May 5, had been more profuse than usual and had been followed by intermittent episodes of spotting. The day prior to admission the patient had passed some clots. She believed that she was pregnant, having subjective symptoms reminiscent of her previous pregnancy. A tentative diagnosis of an incomplete miscarriage was made, and a urine sample was obtained on the day of admission. The Aschheim–Zondek test was positive, and the frog reaction was negative.

Because of the persistence of the vaginal bleeding, a curettage was performed on June 10. The report was as follows: "Decidua-like cells; no definite chorionic villi." The lower abdominal pain persisted, and on July 6 an exploratory laparotomy revealed a left-sided tubal pregnancy. Three days later hormone tests were again performed, and both the rat and frog reactions were negative.

In contrast to this case, it is interesting to note that in another ectopic pregnancy not unlike it, in which the frog test was correct, the period of conception was only five weeks.

The shortest duration of pregnancy detected by the frog test occurred in the normal-pregnancy group and was positive five days after the first missed period. Since the patient followed a relatively exact twenty-eight-day cycle, it seems fair to assume that the duration of gestation must have been not more than twenty days.

Discussion

As can be seen from the preceding results, no false-positive diagnoses were encountered throughout the series. This finding has been corroborated by many previous investigations.[4, 5] In 4 cases, the frog method gave a false-negative result. The clinical follow-up of these patients showed that in each case the hormone titer of the urine had undoubtedly been low. In the 2 cases of ectopic pregnancy, it is likely that the viability of the products of conception had been impaired, at least to some degree, before the urine sample was obtained, because an equally early ectopic pregnancy in another patient gave a clear-cut positive result with the frog test. In the other 2 cases in which the results with the frogs were incorrect, the patients were in all probability in the process of miscarrying at the time the urine was obtained, and with the death of the chorionic epithelium the hormone levels had fallen to critically low levels.

Table 1. *Results of Frog Tests.*

Clinical Diagnosis	Results			
	Correct Positive	Correct Negative	False-Positive	False-Negative
Possible pregnancy	40	41	—	—
Suspected ectopic pregnancy	4	—	—	2
Miscarriage	1	7	—	2
Abdominal tumors with possible concomitant pregnancy	—	3	—	—
Totals	45	51	0	4

During the later stages of this series, with increasing experience, it became apparent that these inaccuracies could be avoided, in large part or entirely, by one of several modifications of the original technic, and in the last 78 cases of the series no discrepancies were encountered. Thus, on one occasion, when a pair of frogs received equal volumes of the same urine, one animal responded with the extrusion of eggs and the other frog failed to react, even after twenty-four hours had elapsed. After the passage of another twenty-four hours the latter frog became positive, demonstrating either an extremely low hormone titer in the urine, to which one animal was more sensitive than the other, or a sluggish physiologic response on the part of the late-reacting frog. Therefore, the rare false-negative result can often be avoided by observing all test animals for forty-eight hours.

In an effort to minimize further these false-negative reactions in cases of suspected low titer, we have recently resorted to the use of a concentrate from a larger volume of urine (80 cc.), and have as yet encountered no ill effects on the frogs. In the case of the twenty-day period of pregnancy, parallel

injections of a 40-cc. and an 80-cc. concentrate were made into two pairs of frogs. The animals receiving the larger volume reacted much more vigorously, giving strong positive reactions, whereas the other pair gave extremely weak positive reactions.

It is to be hoped that, with these larger amounts of urine, levels of hormone can be detected that will make the frog test compare favorably in sensitivity with the rat test. It must be acknowledged, however, that when the original technic is followed the frog, although never giving false-positive reactions, appears to be somewhat less sensitive than the immature rat. On the other hand, since adoption of the modifications mentioned above, false-negative reactions in urines of extremely low titer have been avoided.

SUMMARY

The extrusion of eggs by the South African clawed frog on stimulation by mammalian gonadotropic hormones, such as are excreted in the urine of women during pregnancy, offers a desirable test for pregnancy. Among its advantages are speed, since ordinarily only eight to twelve hours are required for a positive reaction; ease in the performance and reading of the test; economy, since the animals can be reused over a period of many years; and simplicity in feeding and maintenance of the animals, since they require no elaborate or separate animal rooms.

In a carefully controlled series of 100 consecutive routine urine analyses, the test gave no false-positive reactions, but in 4 cases of low-titer urines it failed to give a positive reaction. It is believed that with minor modifications in the original technic these false-negative reactions can be avoided and that this test can be made to compare favorably with the older, more widely accepted rabbit, rat and mouse tests. The rapid diagnosis that it affords is desirable in general, and in cases presenting difficult diagnostic problems this factor may be of great value in indicating the correct therapeutic procedure to be adopted.

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THE ORAL LESIONS OF MONOCYTIC LEUKEMIA*

Report of a Case

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IN REPORTING this case of subacute monocytic leukemia, the oral lesions are particularly stressed, since they dominated the clinical picture almost from the onset of the blood dyscrasia.

Oral lesions represent a frequent and early finding in the various types of leukemia, especially in the acute forms. In monocytic leukemia, which represents 5 per cent of all the cases of leukemia, gingival and other oral changes occur in an extremely high percentage of cases except in edentulous mouths. Indeed, much of the suffering experienced by the patient in monocytic leukemia is related to the pain and discomfort from the necrotic and ulcerative lesions of the gingival and buccal mucosa, the highest percentage of lesions being found in the acute cases. Love[1] reported 82 of 152 cases of various types of leukemia with oral lesions. The most frequent sign was bleeding from the gums, with swelling, necrosis and ulceration of the gingivae. Forkner[2] states that in acute monocytic leukemia acute swelling of the gingivae with a tendency for the teeth to become submerged in the gums is encountered in the great majority of cases. He believes that the infiltrative lesions of the gums are always pathognomonic of acute monocytic leukemia. Osgood[3] reviewed a series of cases of monocytic leukemia and reported that gingival swelling was noted in 80 per cent of 88 cases in which the gums were mentioned. Klumpp and Evans[4] report that of 8 cases of monocytic leukemia 5 were discovered following extraction of the teeth, and conclude that oral lesions are frequent in acute leukemia and are prone to occur early in the disease. Moloney[5] in reporting 9 cases of leukemia found that 7 patients first visited the doctor or dentist because of bleeding from the gums, "trench mouth" or pain in the jaw. He concludes that palliative measures and the avoidance of injudicious oral surgery make the patient much more comfortable.

There are many other causes of gingival hyperplasia with edema, necrosis and a tendency to bleed from the gums, either spontaneously or from slight

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trauma. In the treatment of epilepsy with dilantin extreme cases of gingival hyperplasia, in many of which the teeth are completely obscured, occur in about 50 per cent of patients.[6] The hyperplasia develops principally on the labial aspect of the gingivae in these cases. In all cases of Vincent's infection of the gingivae, with its associated redness and necrosis and fetid breath, it is desirable to make an examination of the blood to rule out a severe blood dyscrasia. Aplastic anemia, agranulocytosis, infectious mononucleosis and reaction to many drugs may cause acute gingival necrotic lesions similar to the lesions found in leukemia. The blood picture, together with other physical findings, should enable one to differentiate the etiologic factors in these cases.

FIGURE 1. *Photograph of the Teeth and Gums.*
Note the marked hyperplasia of the gingiva, which almost completely obscures the lower cuspid teeth.

L. T., a 27-year-old woman, was admitted to the Quincy City Hospital on February 3, 1945. The family history was negative. The patient's parents, both of two brothers and a sister were living and well. She had had no previous serious illness and had the usual children's diseases at an early age.

Three months previously the patient had first complained of a severe headache, which was located in the orbital, frontal and occipital regions. There was an associated inflammation of the eyelids, with a slight exudate. There was chronic nausea with occasional attacks of vomiting almost from the beginning of the illness, and a weight loss of 50 pounds in 3 months. The patient was admitted to the Clinic Consultation Service of the Pratt Diagnostic Hospital on January 3, 1945, and was discharged on January 18. On entrance there she appeared quite sick, and in addition to bleeding and swollen gums showed swollen eyelids, with a mild conjunctivitis. Physical examination revealed marked emaciation, with extreme pallor of the skin. The liver and spleen were not palpable, and the chest was clear of rales. The white-cell count was 17,530, with 33 per cent mature neutrophils, 3 per cent metamyelocytes, 1 per cent myelocytes, 2 per cent myeloblasts, 1 per cent eosinophils, 28 per cent lymphocytes and 32 per cent monocytes; 2 histiocytes were seen. Oral examination revealed a marked hypertrophic condition of the gingival papillae. They were extremely soft and spongy and bled easily when touched. A sternal puncture yielded an almost pure culture of large monocytic cells, with an extreme reduction of the normal cellular elements of the marrow. A diagnosis of subacute monocytic leukemia was made. During the patient's stay the course of the illness was progressively downhill, although there were temporary responses to transfusions and injections of a bone-marrow stimulant. The patient ran a spiking temperature up to 102°F. during the hospital course, and the gums failed to respond to radiation therapy.

On entrance to the Quincy City Hospital 3 months after the onset of the disease, the oral condition was further advanced (Fig. 1). The patient complained particularly of the pain and discomfort in the mouth. There was dysphagia and increased salivation but no bleeding from the gums. A pronounced fetid odor to the breath similar to the odor found in cases of acute Vincent's infection was present. There was a moderate swelling of the gums, which were bright red and edematous, with elongation of the interdental papillae. A superficial grayish slough was noted at the borders of the papillae, similar to that seen in acute Vincent's gingival infection.

Smears taken shortly after entrance revealed a rich bacterial flora, with Vincent's spirochetes and fusiform bacilli predominating. The teeth appeared to be in good condition, with the exception of the superior left 1st molar, which showed extensive caries. The buccal mucosa showed generalized reddening, but no areas of necrosis or purpuric lesions were noted. The cervical lymph nodes were moderately enlarged, especially in the submental and submaxillary regions, and palpation of these nodes elicited moderate tenderness.

There was progressive involvement of the tissues of the oral cavity until death, which occurred on March 14, in spite of local and constitutional treatment, including multiple

blood transfusions. The hyperplastic gum tissue increased in size along both the labial and lingual surfaces of the alveolus. The entire arch became broad and was made up of swollen, edematous, necrotic, vascular gingival tissue that gradually obscured the teeth. Three or 4 weeks after the initial examination, a secondary growth of hyperplastic tissue developed at the base, following the same pattern as the outer layer and increasing the width of the alveolus to such an extent that the palatal vault was all but eliminated. The floor of the mouth above the myohoid ridges was also partially filled with vascular, necrotic gingival tissue, so that the tongue was raised and there was inability to close the mouth.

The mouth remained extremely dry, partly owing to evaporation, and new superficial necrotic lesions of the mucosa developed, with secondary gangrenous changes. These areas, which were located on the lateral margins of the tongue and the buccal mucosa of the cheeks, were covered by a pale-yellow pseudomembrane, which on peeling left a raw, bleeding surface. There was an ulcerated lesion on the right lateral palatal region near the 1st molar tooth and another involving the left side of the soft palate and extending to the anterior pillar of the fauces. Four days before death, fairly generalized petechial and purpuric macular lesions appeared on the buccal mucosa, concomitant with similar hemorrhagic lesions of the skin over the face. Inspissated blood, mucus, detritus and exudate formed a hard shell on the dorsum of the tongue. This deposit was softened and removed daily. Following the formation of the secondary hyperplastic gum tissue, the teeth tended to migrate and to assume fantastic positions in the arch, indicating destruction of the alveolar lamina dura.

A biopsy specimen taken from an interdental papilla showed the following histologic picture. The outer labial stratified epithelial surface was thinned out, especially in the prickle-cell layer. There was considerable edema of the underlying tunica propria, with increased capillary vascularity. There was a wide zone of edematous fibroblastic connective tissue moderately infiltrated with monocytes and cells of the lymphoid type, with rare polymorphonuclear leukocytes. The monocytes represented 50 per cent of the infiltrating cells. Deeper in the specimen was less edematous and more pronounced cellular tissue, consisting principally of closely packed monocytic cells with a few lymphocytes. The large vessels were choked with monocytes. The dental surface of the gum tissue showed marked necrosis, with absence of the epithelial surface layer. The infiltration of monocytes was especially pronounced, and there were numerous foci of hemorrhage. This portion of the specimen represented the site from which a rich bacterial flora and Vincent's organisms were demonstrated on smears.

The local treatment to the oral cavity given by one of us (P.H.K.) consisted of irrigations with warm normal saline solution, which tended to keep the exudate softened and helped in removing the pseudomembrane from the necrotic surfaces of the gingival and buccal mucosa. This procedure was frequently used during the daytime and gave considerable relief from the pain and dryness in the mouth. Zinc peroxide dusted into the deep recesses of the necrotic and hyperplastic tissue, especially after eating, and neoarsphenamine in glycerin — 0.8 gm. to 30 cc. of glycerin — swabbed into the necrotic pockets helped to control the secondary invasion of Vincent's organisms. Six-millimeter gauze strips saturated with oil esthesin, an oil-base surface anesthetic, placed in the superior and inferior vestibule of the mouth three times daily after eating controlled much of the pain. Hyperplastic necrotic and gangrenous tabs of tissue were cut away with a scalpel and curved scissors, giving much relief. Vaseline smeared on the lips and commissure kept them soft.

Autopsy. The body was that of a fairly well developed and poorly nourished young woman. The scleras and skin had a moderately icteric tinge. There were purpuric and petechial hemorrhages on the face, especially the alae nasi, and the forearms. There were recent organizing fibrinous adhesions binding the right lung to the chest wall and obliterating the pericardial sac.

In the upper half of the lower lobe of the right lung, there were multiple miliary abscesses surrounded by areas of consolidation up to 1 cm. in diameter. Both the spleen and the liver were enlarged, and the malpighian bodies in the spleen were barely visible. The kidneys were remarkable in appearance. Their combined weight was 360 gm. Removal of the capsules revealed smooth, canary-yellow cortical surfaces with an average thickness of 1.2 cm. The line of demarkation between the cortices and pyramids was barely discernible, and there were multiple petechial and large hemorrhagic foci throughout the parenchyma of both kidneys and also in the pelves. There was no evidence of adenopathy in the cervical, axillary and inguinal nodes.

Microscopical examination of the viscera revealed the following. *Kidneys*: The tubular epithelium took the stain extremely faintly, and many of the cells show only nuclear staining. There was a diffuse cellular infiltration of the connective tissue with monocytes and lymphoid cells. The convoluted tubules showed the most pronounced evidence of epithelial degeneration. Hyaline casts were demonstrated in the tubules throughout the specimen. The long, straight veins of the pyramids were congested. Focal areas of hemorrhage occurred in the cortex and pyramids. *Spleen*: The spleen showed a diffuse infiltration with monocytes and cells of the lymphoid type and rare eosinophils. Phagocytic cells containing brownish granular pigment were diffused throughout the pulp. The capillaries were dilated with focal areas of hemorrhage. The malpighian bodies were small and disorganized. *Liver*: The interlobular connective tissue of the liver showed a marked cellular infiltration, principally monocytic. The capillaries and sinusoids revealed similar infiltration. The capsule and subcapsular space showed an extreme monocytic cellular infiltration. The liver cells took the stain extremely faintly, and many contained vacuoles. There was a moderate proliferation of the bile ducts. Focal areas of hemorrhage occurred throughout the organ. *Lymph Nodes*: The architecture of the lymph nodes was obliterated, although the germinal centers of the lymph follicles were discernible. There was a diffuse infiltration of the nodes and capsules with monocytic cells and lymphoid cells (Fig. 2).

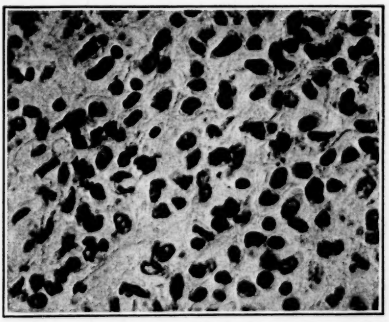

FIGURE 2. *Photomicrograph of a Section of Lymph Node Showing Diffuse Infiltration with Monocytic and Lymphocytic cells.*

No polymorphonuclear leukocytes or eosinophils were demonstrated. *Bone Marrow*: The bone marrow of the rib showed a significant reduction in the normal cellular components. There was a marked increase in monocytes, which represented 80 per cent of the total cells. A few myelocytes, lymphocytes and nucleated red cells were demonstrated. *Blood*: A stained smear showed lymphocytes and monocytes, with relatively few polymorphonuclear cells (Fig. 3).

The anatomical diagnoses were as follows: subacute monocytic leukemia; acute hemorrhagic nephritis; fatty degeneration and infiltration of the liver; subacute adhesive pericarditis; splenomegaly; septic bronchopneumonia of the right lung; icterus; purpura hemorrhagica; hyperplastic stomatitis, with necrosis and purpura; ulcerative enterocolitis; monocytic hyperplasia of the bone marrow; and monocytic infiltration of the viscera.

Lesions of the oral mucosa with extensive involvement of the gingivae represent important complications in acute and subacute monocytic leukemia, particularly since much of the suffering is caused by them. It is desirable that the dental consultant take over the management and treatment of the case as it relates to the mouth, and that he apply the treatment either personally or under direct supervision so that the patient may be relieved of the intense discomfort attending these cases. In all cases of gingival hyperplasia with bleeding and a tendency to necrosis, with secondary Vincent's infection, blood examinations should be made to rule out serious blood dyscrasias.

Summary

A case of subacute monocytic leukemia is described, with special reference to the oral lesions. Treatment of these lesions by the dental consultant was helpful in relieving the acute symptoms in this case.

In monocytic leukemia, involvement of the oral cavity occurs more frequently than in any other type of leukemia and is often an early manifestation.

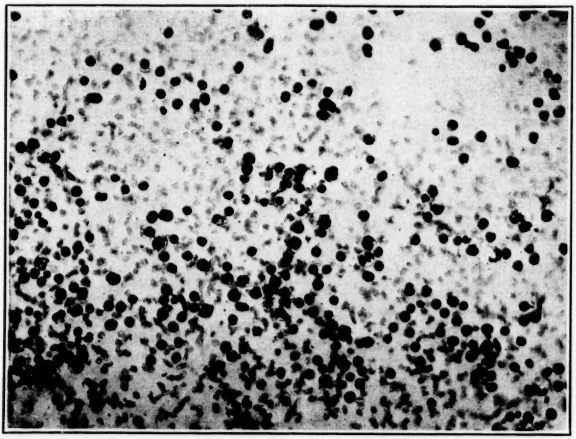

FIGURE 3. *Photomicrograph of a Blood Smear Showing Lymphocytosis and Monocytosis but Relatively Few Polymorphonuclear Leukocytes.*

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MEDICAL PROGRESS

FLUORINE AND DENTAL CARIES (Concluded)

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BOSTON

EFFECT OF FLUORINE ON DENTAL CARIES

THE earliest references in the literature on the relation of fluorine to dental caries were made in 1916 by McKay and Black,[56, 57] who studied the so-called "Colorado brown stain." During the following decade mottled enamel and dental caries were extensively studied by McKay[58, 59] and Bunting et al.[61] It was not until 1931, however, according to Dean[60] that fluorine was discovered as the cause of mottled enamel. Four methods were used in studying the cause, prevalence and control of mottled enamel and the lowered prevalence of dental caries in certain areas. These consisted in refinements in measuring the rates of prevalence of caries in relation to age, sex and race[3, 61]; elimination of the circulation factor, or limitation of observations to persons continuously exposed to the specific environment factor under investigation — the common water supply[62]; the development of a chemical method permitting water analyses that were accurate to 0.1 part per million of fluorine[63]; and the development of quantitative methods for estimating the number of *Lactobacillus acidophilus* in saliva, this being used as an index of the activity of dental caries.[64]

The role of fluorine in dental health is ably described in a monograph entitled *Fluorine and Dental Health*, a publication of the American Association for the Advancement of Science edited by Moulton.[65] Another important monograph, entitled *Fluorine in Dental Public Health*,[66] is the report of a symposium at the ninety-fourth monthly conference of the New York Institute of Clinical Oral Pathology, held in New York City in 1944. Finally, by resolve of the General Court, the Massachusetts Department of Public Health[67] prepared in 1945 a monograph entitled *Special Report Relative to the Decay of Teeth Resulting from a Lack of Fluorine.*

Mottled Enamel

Following the original work of McKay[66] in discovering the condition now called mottled enamel, surveys were made in other communities in which discolored teeth were prevalent.[68] The relation of mottled enamel to water supplies from deep wells had been established as long ago as 1918 by the same author,[69] but it was not until 1932 that the fluorine content of water supplies was related to this condition.[70] In 1928, the United States Public Health Service undertook to investigate mottled enamel and deformity of teeth of children at Bauxite, Arkansas. The Aluminum Company of America,[71] which owned a mine near which the town was located, caused samples of water to be examined in its laboratory. This examination disclosed that the water from the deep wells supplying the town contained an unusually high content of fluorine. Soon similar findings revealed that a water supply of a high fluorine contact was a common factor among children who had developed mottled enamel. Examination of water supplies in communities in which no mottling was found revealed that fluorine was present in extremely small quantities, less than two parts per million.

It was recommended that Bauxite obtain a water supply that did not contain fluorine,† and this was done. In 1938, ten years after the town had begun taking water from the Saline River, which contained practically no fluorine, Dean[74] and others[75] reported that all children who had used the water from the deep wells during infancy and early childhood showed mottled enamel. On the other hand, the same children exhibited a low incidence of dental caries, even though they had been using fluorine-free water for twelve years. In contrast, children living in the nearby town of Benton, who had used Saline River water throughout their lifetime, showed no mottling of enamel but a high prevalence of dental caries. Other evidences of the beneficial effects of fluorine were also found. Children of Bauxite who were born within a few years after the change in water supply and had therefore used the old water for only three or four years showed practically no mottling but had a low incidence of dental caries. The children born after the new water supply was obtained showed the highest caries index. Similarly, mottled enamel has been eliminated at Oakley, Idaho, and Andover, South Dakota, by changing the water supply from one containing amounts of fluorides toxic to calcifying dental enamel to one with a fluoride content not

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†Numerous attempts[72, 73] have been made to remove excess fluorine from water supplies by using tricalcium phosphate, magnesium oxide or magnesium hydroxide. Of these chemicals, magnesium oxide is the least expensive; the commercial light grade is better than the commercial calcined one, but its higher cost is not in proportion to its greater efficiency. It may be stated that whenever possible it is better to obtain a new water supply containing only 1 p.p.m. (part per million) of fluorine than to attempt defluorination.

exceeding 1 p.p.m.[76] The unusually long interval in time, eight to ten years, before the clinical effects resultant from a change in the water supply may be observed clinically, is unique in epidemiologic investigations of water-borne diseases.

Communities seeking new water supplies[77] in areas where deep wells are required should have detailed chemical analyses performed before making the new supply available to the public. The city of Narka, Kansas, developed two new deep wells 262 feet deep; the water from these contained 1.2 and 1.3 p.p.m. of fluorine, respectively. Epidemiologic investigation of private water supplies from deep wells in the areas surrounding the new wells, however, showed that 8 children who were raised on these private supplies containing 0.8 to 3.0 p.p.m. of fluorine had not developed mottled enamel. Hence, the new supply was made available.

Fluorine-Containing Water Supplies and Dental Caries

Meanwhile, other studies had been in progress to determine how much benefit fluorine exerted in the prevention of dental caries. The South Dakota studies made by Dean and McKay[76] in 1938 showed sharp differences in the prevalence of dental caries, depending on whether the population was affected with dental fluorosis. Dean and McKay's article contains a report on the examination of 236 nine-year-old children with a verified continuity of exposure to the fluorine-containing domestic waters of the cities in which they lived. It was noted that there was relative freedom from dental caries in deciduous teeth as well as permanent teeth, whether or not the teeth showed macroscopic evidence of mottled enamel. In 1939, Dean et al.[78] and others[79] reported a study of four cities in Illinois. In Galesburg and Monmouth, where the water contained 1.8 and 1.7 p.p.m. of fluorine, respectively, the children examined showed an average of 2.0 DMF teeth per child. In Macomb and Quincy, where the water supplies contained only 0.2 p.p.m. of fluorine, the children showed an average of 4.0 and 6.3 DMF teeth, respectively.

Another study was made by Dean and others[80] to determine the lowest concentration effective in reducing the incidence of dental caries and the magnitude of this inhibition. Eight suburban cities around Chicago were selected. The water of Elmhurst, Maywood, Aurora and Joliet had 1.8, 1.2, 1.2, and 1.3 p.p.m. of fluorine, respectively. Elgin was intermediate, with 0.5 p.p.m., and Evanston, Oak Park and Waukegan used fluorine-free water. The prevalence of dental caries in these eight cities, expressed as an average of the number of DMF teeth per child, was as follows: Elmhurst, 2.5; Maywood, 2.6; Aurora, 2.8; Joliet, 3.2; Elgin, 4.4; Evanston, 6.7; Oak Park, 7.2; and Waukegan, 8.1.

It will be seen that children living in the communities using water with the higher fluorine content had markedly less dental caries than did those living in communities using fluorine-free water, and that 0.5 p.p.m. was not sufficient to give appreciable protection. The populations in these cities were so nearly similar from other points of view that it is difficult to ascribe these differences in the prevalence of dental caries to any other cause than the differences in the concentration of fluorine in the water supply. Moreover, the inhibiting effect was exhibited at such a low concentration that mottled enamel as an esthetic problem was not encountered.

In another study,[81] including examinations of children in twenty-one cities in four states, the level at which the inhibiting factors operate was made even clearer (Table 3). It will be noted that there was a marked drop in the beneficial effect when the concentration was under 0.5 p.p.m. of fluorine, and that there was no appreciable increase in the inhibiting effect when the concentration was above 1.4 p.p.m.

Table 3. *Relation of the Prevalence of Dental Caries to the Fluorine Content of Water Supplies.*

Fluorine Concentration of Water Supply	No. of Cities	No. of Children Examined	No. of Permanent Teeth Showing Dental Caries per 100 Children
p.p.m.			
Less than 0.5	11	3,867	700+
0.5 to 0.9	3	1,140	400+
0.9 to 1.4	4	1,403	300
More than 1.4	3	847	250

The mechanism whereby this element contributes to the prevention of dental decay is thought to be primarily one of increased fluorine content of the tooth enamel.[82] This may result from incorporation of fluorine in the tooth during the period of tooth formation or by acquisition of fluorine from the external surface of the tooth after eruption. There is an affinity between the calcium phosphates of the tooth and fluorine. This fluorine increment in the enamel makes the tooth less soluble in acids. Also, in an environment of fluorine the acid and bacteria in the vicinity of the teeth are reduced. Thus, it seems that at least one substance has been found that successfully counteracts the effects of acids produced by the growth of bacteria in the presence of carbohydrates.

Addition of Fluorides to Public Water Supplies

Since it has been demonstrated that fluorine found naturally in water supplies combats the inroads of dental caries, one of the first practical questions that arise is whether this useful element can be purposely supplied in areas where it is absent from or extremely low in the water supply. Any domestic water supply, so far as its fluoride content influences dental health, may be thought of as falling into one of three classes — water supplies naturally

with the optimal concentration of fluorine (about 1.0 p.p.m.); water supplies with an excess of fluorine, requiring its removal to protect the population against endemic dental fluorosis (mottled enamel) or its replacement by or mixture with other water supplies low in fluoride; and water supplies deficient in fluorine, to which it might be added to bring about an optimal concentration of this element so as to lessen the amount of dental decay.

Several states have made detailed analyses of the fluorine content of public and semipublic water supplies. New Jersey has six communities with public water supplies having a fluorine content between 1.0 and 2.4 p.p.m. This survey, conducted by Wisan,[83] revealed that children in these communities had a lower caries rate than children living in communities serviced with fluorine-free water. Extensive studies have been made of water supplies in Florida,[65] Illinois,[65] Indiana,[84] Louisiana,[85, 86] Nebraska,[65] New Mexico,[87] North Dakota,[88] Ohio,[89] South Dakota,[90, 91] Texas,[92] Utah,[65] Virginia,[93] and Wisconsin[65, 94] and in 1945 complete mineral-water analyses were made of all public and semipublic water supplies in Massachusetts.[67] The literature contains many references to the finding of endemic fluorosis in Argentina, Australia, China, Chosen, Ecuador, England, Greenland, India, Malaya, Mexico, Java, South Africa, Tristan da Cunha and Western Asia (Iraq, Trans-Jordan, Syria, the Bahrein Islands, Arabia and Palestine).[65]

The present standard for fluorine content of public water supplies, as defined by the United States Public Health Service, calls for the rejection of the water supply if it contains more than 1.0 p.p.m. The recommended methods of analysis of water supplies are those contained in *Standard Methods for the Examination of Water and Sewage* of the American Public Health Association and a committee report, "Methods of Determining Fluorides," that appeared in 1941 in the *Journal of the American Water Works Association*.[95]

A circular letter from the United States Public Health Service to the Advisory Committee on Drinking Water Standards,[96] on the tentative revision of the 1942 standards, recommends that the presence of fluorine in excess of 1.5 p.p.m. shall constitute grounds for rejection of the supply.

Massachusetts[67] waters contain extremely small concentrations of fluorine. The maximum quantity found in any one sample was 1.2 p.p.m. in the semipublic supply at Farnumsville in Grafton. Unfortunately, the number of children who continuously used this supply was too small to justify any conclusions relative to the effect of the fluorine on the caries rate. Fluorine concentrations of 1.0 and 0.7 p.p.m., respectively, were found in deep wells used only as auxiliary water supplies at Lyonsville in Colrain and at Fisherville in Grafton, but the regular water supplies of these communities were low in fluorine. Of 368 samples analyzed, 359 (98 per cent) contained 0.2 p.p.m. or less, and 229 (62 per cent) contained 0.1 p.p.m. or less. The average of all samples was 0.11 p.p.m., an amount that is far below the optimal 1.0 p.p.m. that is effective in lessening dental caries.

Sodium fluoride may be added in correct amounts to a water supply. Ast[66] describes a plan to determine the practicability, efficacy and safety of fluorinating a communal water supply deficient in fluorine to control dental caries. Three communities are now conducting such studies — Grand Rapids, Michigan,[97] Newburgh, New York[66] and Marshall, Texas.[98]

TABLE 4. *Data on Topical Application of Fluoride.*

PLACE AND AUTHOR	CHILDREN NO.	CHILDREN AGES	NO. OF TREATMENTS PER YEAR	STRENGTH OF FLUORIDE SOLUTION	REDUCTION IN CARIES RATE
		yr.		%	%
Brockton, Mass. (Bibby[99])	90	10–13	3	0.1 (NaF)	46
Indiana (Cheyne[100])	46	4–6	2 (in 4 mo.)	0.05 (KF)	50
Minnesota (Knutson and Armstrong[101])	289	7–15	7–15 (in 8 wk.)	2.0 (NaF)	40
Coast Guard (Arnold et al.[102])	188	17–22	1	1.0 (NaF—acidulated)	0
Cambridge, Mass. (McKelleget and Bibby[103])	47	6–14	3	1.0 (NaF)	43
Millville, Mass. (Labunsky and Bibby[103])	91	6–14	2	1.0 (NaF)	25

TOPICAL APPLICATION OF FLUORIDES

Because it was suspected that fluorine could act directly on the teeth through the external surface, one of the first methods of using fluorine was the application of solutions of sodium fluoride directly to the teeth, either in the mixtures used in cleaning the teeth or in simple solutions after such cleaning had been performed by dentists and their assistants.[66] The results of a few of these studies are shown in Table 4.[97]

It will be seen that when these applications are made in children of the youngest age groups, the caries reduction varies from 25 to 50 per cent and that similar applications in adults produce little effect. Undoubtedly, when the proper concentration of solutions and the optimum number of appli-

cations have been determined, one can expect the caries reduction to be regularly over 50 per cent. The principal drawback of this method of the use of fluorine is that it must be carried out in the dentist's office or under the supervision of a dentist, and that the results will be limited by the fact that there are not sufficient dentists and dental assistants[104] available to give treatments to all of the persons in the areas in which the fluorine content of the water supply is low. Other methods of using fluorine must therefore be found to supplement direct applications in the dentist's office. At the present time, studies are in progress in various states to determine whether fluoride added to mouthwashes or dentifrices exerts a beneficial effect.

Fluorine in Foods

The question has been raised whether sufficient amounts of fluorine can be obtained from food materials to exert a beneficial effect. This matter has been investigated by a number of workers.[105, 106] It has been found that most foodstuffs contain extremely small quantities of fluorine. As would be expected, the quantities are somewhat increased in high-fluorine areas, particularly if vegetables are irrigated or sprayed with water containing fluorine. The supply of foodstuffs coming from such areas, however, constitutes such a small portion of the total quantities used that the general level of fluorine is not raised to any significant degree. It has been found that fluorine is excreted in the feces, urine and sweat in sufficient quantities so that the amount obtained from food supplies is lost so promptly that no beneficial effects can be expected.[107] The only food materials with a high quantity of fluorine are those that contain bone or bone meal, such as small fish the bones of which are consumed or baby foods to which bone meal has been added. It has been observed that certain primitive peoples who depend largely on fish for protein show a low attack rate of dental caries. It may be that this is due to the fluorine in the bones of the fish.

Although this field has not been thoroughly explored, it appears likely that persons living in modern American communities will not receive much benefit from fluorine obtained from food supplies. If it is eventually demonstrated that the beneficial effect of fluorine is due to the local contact when water flows over the teeth and not to the fact that fluoride is assimilated by the blood supply, this may further explain why fluorine in foods is not more effective, since it is not so easily available for a local effect, being intimately bound up with the foods.

* * *

It will be seen from the foregoing discussion that all practitioners of the healing arts have good season to believe that fluorine exerts a direct beneficial effect in preventing dental caries. It may even be that the higher prevalence of dental defects in New England, as well as elsewhere, can be ascribed to the absence of this useful chemical. If this proves to be the case, the simple addition of fluoride to water supplies or to other materials widely used by the public may exert a profound effect on this public-health problem. It is important, however, that fluorine be used judiciously, because it not only exerts a beneficial effect but if used in excess may have a deleterious effect on the teeth. Care must therefore be employed against supplying the chemical in amounts large enough to produce dental fluorosis.

There are probably many factors that affect the action of fluorine that are yet to be investigated. For instance, it has been noted that in northern India, where the fluorine content of the water supply is high and the general diet is superior, the natives do not develop fluorosis.[108] On the other hand, the condition is frequently seen in southern India, where the diet is much less adequate and the fluorine content of the water is no higher. Susceptibility to fluorosis therefore seems to increase through lack of certain essential nutrients.

Current Research on Dental Caries and Fluorine

Further studies are necessary to determine the best methods for utilizing this useful chemical. To learn of any research recently begun or in progress in other states that has not yet been described in public-health and dental journals, letters were sent to all the health officers of the states and provinces of the United States and Canada asking for such details as were available. Attention was called to the fact that the Massachusetts Department of Public Health was particularly interested in research regarding the effect of fluorine. The information obtained is summarized in Table 5, and a short description of the projects in a few of the states follows.

Alabama. Studies are being conducted in establishing prevalence rates for dental disease. The Department of Geology of the University of Alabama is making a study of the groundwater supply, financed by the State Health Department, to determine the amount of sodium fluoride it contains. State-sponsored clinics will utilize topical applications of sodium fluoride on half of a series of patients, the other half serving as controls. Further work on the use of fluoride in topical applications will be carried on, the state dentist working in collaboration with the Department of Geology of the University of Alabama.

California. Drs. Becks and Wainwright, of the California Dental College, have carried out studies on the relation of *B. acidophilus* to dental caries. Becks and his co-workers are also studying the effect of fluorides on dental tissues.

Connecticut. Projects have been set up to show the local effects of fluorides on tooth structures. These include the study of the effect of adding fluoride to the water supply of the Southbury Training School; tooth analyses are being made

Illinois. Plans are being made for a study of the use of fluoride in the public water supply as a dental decay preventive in Evanston. Previous work has been done by the United States Public Health Service on the relation between dental caries and

TABLE 5. *Dental Caries Research Programs in the United States and Canada, 1945.*

STATE OR PROVINCE	SURVEY OF FLUORINE IN WATER SUPPLIES	ADDITION OF FLUORIDE TO DRINKING WATER	OTHER FLUORIDE STUDIES (TOPICAL APPLICATION, ETC.)	OTHER DENTAL-CARIES STUDIES
Alabama	In progress	—	Planned	Prevalence rates
Arizona	—	—	—	—
California	—	—	In progress	Bacterial counts
Connecticut	In progress	In progress	In progress	Prevalence rates and bacterial counts
Delaware	—	—	—	—
Florida	—	—	—	Prevalence rates
Georgia	—	—	—	Prevalence rates
Idaho	—	—	—	Prevalence rates
Illinois	Completed	Planned	—	Prevalence rates
Indiana	Planned	Planned	Planned	Prevalence rates
Iowa	In progress	—	—	Prevalence rates
Kansas	In progress	—	—	Prevalence rates
Kentucky	—	—	—	—
Louisiana	—	—	—	—
Maine	Completed	—	—	Prevalence rates
Maryland	Planned	—	In progress	Planned
Massachusetts	Completed	Planned	In progress	Prevalence and incidence rates
Michigan	Completed	In progress	Planned	Prevalence rates
Minnesota	—	—	In progress	Prevalence rates
Mississippi	—	—	In progress	Prevalence rates
Missouri	—	—	—	—
Montana	—	—	—	—
Nebraska	—	—	—	Prevalence rates and bacterial counts
Nevada	Completed	—	—	—
New Hampshire	—	—	In progress	Prevalence rates
New Jersey	—	—	In progress	Prevalence rates, etc.
New Mexico	—	—	—	—
New York	Completed	In progress	Planned	Prevalence rates, etc.
North Carolina	—	—	—	—
North Dakota	Completed	—	—	—
Ohio	Completed	In progress	In progress	Prevalence rates, etc.
Oklahoma	—	—	—	Ammoniacal silver nitrate (topical)
Oregon	Planned	Planned	Planned	Prevalence rates
Pennsylvania	—	—	In progress	Prevalence rates
Rhode Island	—	—	In progress	Prevalence rates
South Carolina	—	—	—	—
South Dakota	Completed	—	—	—
Tennessee	—	—	—	Time-and-cost studies
Texas	Completed	In progress	—	—
Utah	—	—	—	—
Vermont	—	—	—	Prevalence rates and nutrition
Virginia	—	—	—	—
Washington	Planned	—	—	Prevalence rates and bacterial counts
West Virginia	—	—	Planned	—
Wisconsin	In progress	Planned	In progress	Caries studies (general)
Wyoming	—	—	—	—
Alaska	—	—	—	—
Hawaii	—	—	—	—
Puerto Rico	—	—	—	—
Canada:				
Alberta	In progress	—	—	—
British Columbia	—	—	—	—
Manitoba	In progress	—	—	—
New Brunswick	—	—	—	—
Nova Scotia	—	—	—	—
Ontario	In progress	In progress	—	Incidence rate and bacterial counts
Prince Edward Island	—	—	—	—
Quebec	—	—	—	—
Saskatchewan	—	—	—	—

and *B. acidophilus* counts recorded. Topical applications of fluoride are being studied at the County Temporary Home for Children. The effects of a mouthwash containing 5 p.p.m. of sodium fluoride are being examined.

Georgia. Preliminary studies are being made by Dr. Dean, of the United States Public Health Service, in an area low in caries prevalence to ascertain the basis for the low attack rate and its relation to the concentration of fluorine in the water supply.

the fluorine content of the local water supplies in several cities.

Iowa. During the last three years there were conducted oral examinations of 12,000 high-school pupils in areas with water supplies high and low in fluorine. The average DMF rate per 100 children in the high areas was 200 to 300; that in the low areas ranged from 300 to 600.

Kansas. Surveys have been conducted of the distribution of fluorine in city water supplies and the DMF rates of children in the eastern third

and the western third of the state. High rates were found in low-fluorine areas.

Maine. An investigation of the incidence of caries was conducted for a number of years, and a study of the analysis of drinking water was made.

Maryland. A prewar investigation of fluorine in water supplies was begun by the United States Public Health Service but has been delayed until more personnel is added. A statistical study of caries was made.

Massachusetts. Study of the effect of fluorine on decay of the teeth has been authorized by the Legislature, with a small appropriation. Some studies on fluorine had already been begun by the Tufts College Dental School and the Massachusetts Department of Public Health. Surveys of the prevalence of dental caries are in progress. The fluorine content of all public water supplies has been determined. These activities are to be extended with the expansion of dental personnel and formation of a division of dental health.

Michigan. The Department of Public Health and the United States Public Health Service are conducting a pilot program in the utilization of 1 p.p.m. of sodium fluoride in the public water supply of Grand Rapids as a preventive of dental caries. Other projects are being carried on in the field of fluoride therapy and diet at the University of Michigan Dental School.

Minnesota. A pilot study is being made by Dr. Knutson, of the United States Public Health Service, on the topical application in a 2 per cent solution of sodium fluoride in 289 school children. Three other studies are being carried on along the same lines by the Department of Public Health in the towns of Hibbing, Chisholm and Virginia.

Mississippi. Preliminary studies are being carried on by Dr. Hagan, of the United States Public Health Service, in two counties on the effectiveness of topical applications of sodium fluoride.

Nebraska. Studies were made on the relation of *B. acidophilus* to dental caries at Boys' Town.

Nevada. A preliminary study is being made of the production of dental fluorosis by varying high percentages of fluorine in the water supply.

New Hampshire. Two demonstrations are in progress on the topical application of fluoride to tooth structures.

New York. The State Department of Health is conducting a pilot program in the utilization of 1 p.p.m. of flourine in the public water supply of Newburgh. Kingston, across the Hudson River, is used as the control community. Other projects in fluoride therapy are contemplated.

Ohio. The United States Public Health Service has been conducting a fluorine project in Garretsville for the last five years. Fluoride has been added to the water supply in this community. A fluorine study is being conducted in Miami County by the United States Public Health Service; this will include topical applications of sodium fluoride.

Oklahoma. Investigations are being conducted of the value of ammoniacal silver nitrate precipitated with eugenol as a means of controlling incipient caries. The program is both remedial and preventive.

Pennsylvania. Two limited programs are being conducted on the topical effects of sodium fluoride.

Rhode Island. Studies are being initiated in the topical effect of sodium fluoride at the St. Aloysius Orphanage, with the use of a 2 per cent solution of sodium fluoride, and by the Abby Frances Lawton Dental Clinic in Central Falls, under Dr. Bibby's direction. In West Warwick (20,000 population) there is a projected study of all school children in relation to the attack rate of caries and the introduction of fluorine into the water supply.

Texas. Marshall is adding 1 p.p.m. of fluorine to the public water supplies. Jacksonville will be used as a control. This is a pilot program.

Washington. The Washington Department of Health is offering laboratory service to private practitioners for counts of *B. acidophilus* and is making a study of diet in relation to the control of dental caries.

West Virginia. The West Virginia Department of Public Health has suggested a technic to dentists in the topical application of sodium fluoride.

Wisconsin. Preliminary surveys were made to determine the prevalence of dental caries. Further work is progressing on a comparison of the incidence of caries among kindergarten children in two cities — Green Bay, with a fluorine content of 2.3 p.p.m. in the water supply, and Sheboygan, with 0.05 p.p.m. Sheboygan proposes to add fluorine to the water supply. Other studies of long duration are contemplated.

Canada. A study is in progress in Alberta on the relation of mottling of enamel to the low incidence of dental decay. In Ontario, the Department of Health, in co-operation with the Research Department of the Faculty of Dentistry, University of Toronto, is making water analyses and surveys to ascertain the incidence of dental caries. Dental surveys were conducted in two fluorine-free municipalities. Following the survey, one of the municipalities introduced fluoride into the water supply.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 32241

PRESENTATION OF CASE

A forty-nine-year-old housewife entered the hospital because of cramps in the legs and carpopedal spasm.

The patient had apparently been well until three days before entry, when she noticed cramps in the calves of both legs, which gradually increased in severity. She also became nauseated, vomiting several times. The following day the vomiting became worse, and she took bicarbonate of soda, which apparently gave some relief. On the afternoon of admission she first noticed spasms causing the hands to flex sharply. This was accompanied by a sensation of "pins and needles" in the arm muscles but no pain.

The patient had passed a total of only 500 cc. of urine since the onset of her illness, although she had frequency of six or seven times a day and two or three times a night. A urinalysis by a local doctor on the day before entry had shown the urine to be heavy in albumin. The last adequate urine output was four days before entry. There was no history of any other urinary symptoms, although her husband stated that during the previous nine months she had occasionally complained of pain in the left groin and flank. There had been no chronic illness, weight loss, headache, stiff neck or food poisoning. The only drugs she recalled taking recently were stilbestrol, occasional small amounts of phenobarbital, aspirin and Karoid with bile salts.

In the past her health had always been excellent. Her two pregnancies were uncomplicated. She was treated at this hospital for a fistula-in-ano nine years before entry, when the urine showed a ++ test for albumin, with 150 white cells per high-power field, and a specific gravity of 1.026. A year later the specific gravity was 1.027, with eight white cells per high-power field and a + test for albumin. The fistula healed satisfactorily.

Physical examination revealed a flushed, drowsy, moderately obese woman who lay quietly in bed but appeared to be in considerable discomfort. She breathed slowly and quietly. The heart, lungs, and abdomen were normal. The hands showed carpopedal spasm. The calves were tender to compression. There was a strikingly active Chvostek sign. The tendon reflexes were somewhat hyperactive. There was no uremic odor to the breath and no peripheral edema.

The temperature, pulse and respirations were normal; the blood pressure was 135 systolic, 85 diastolic.

Examination of the blood revealed a hemoglobin of 12 gm. and hematocrit of 39. The white-cell count was 5200. The nonprotein nitrogen was 136 mg. per 100 cc., rising to 145 mg. the next day. The serum sodium was 136 milliequiv. per liter, the chloride 85 milliequiv., the cholesterol 121 mg. per 100 cc., the carbon dioxide content 27.7 milliequiv. per liter, the alkaline phosphatase 2 Bodansky units, the phosphorus 9 mg. per 100 cc., the calcium 5 mg. and the serum protein 5.4 gm. A catheterized urine specimen (only a few cubic centimeters) was amber colored and clear, with a pH of 5.5. There was a ++++ test for albumin. The sediment contained rare red cells, 75 white cells, a moderate number of epithelial cells and many granular casts per high-power field. The Sulkowitch test for urinary calcium was positive, and a stool examination was guaiac negative. Repeated urine cultures showed moderate to abundant growth of *Staphylococcus albus*.

A cystoscopy and right retrograde pyelography were negative. An x-ray examination of the chest and abdomen was negative.

The patient appeared markedly improved after intravenous calcium gluconate but despite intravenous saline and glucose failed to pass more than a few cubic centimeters of urine at a time. After cystoscopy the urine became grossly bloody. Penicillin effected no improvement. The nonprotein nitrogen continued to rise, reaching 225 mg. per 100 cc. on the fifth hospital day, when peritoneal lavage with a solution of glucose, sodium chloride, sodium lactate and gelatin was instituted at the rate of about thirty liters a day. By the eighth hospital day the nonprotein nitrogen had dropped to 115 mg. per 100 cc., but the temperature began to rise, and the patient developed a cough productive of small amounts of tenacious mucus. On the tenth hospital day she became disoriented and restless, and the temperature spiked to 105°F. On the ninth hospital day the abdomen was found to be distended and tender, although not particularly rigid. A few rhonchi were heard at the lung bases, and there was a pericardial friction rub. The blood pressure had dropped to 60 systolic, 35 diastolic. Abundant colon bacilli and nonhemolytic streptococci were grown from the peritoneal lavage fluid. The nonprotein nitrogen was 78 mg. per 100 cc. Despite continued administration of penicillin, the patient died on the eleventh hospital day.

Differential Diagnosis

Dr. Bernard Jacobson: May we see the films of the pyelogram?

Dr. Tracy B. Mallory: There is no roentgenologist here, but Dr. Lingley reports that the films are entirely negative.

Dr. Jacobson: To me, at least, one of the most disappointing findings in this case is the normal pyelogram. It upsets a good many possibilities that I should like to entertain. There is no evidence of any postrenal obstruction. I assume that the findings on the left side would have been similar had a left retrograde pyelogram been done. It looks like a good x-ray film to me. Do you agree, Dr. Colby?

Dr. Fletcher Colby: We did not do a bilateral pyelogram because the patient was in a precarious state at that time. We were interested in demonstrating, if we could, the presence of at least one normal kidney, which we succeeded in doing. This pyelogram was interpreted as being entirely normal.

Dr. Allan M. Butler: The history mentions pain in the left groin and flank. In view of the history I should like to know why a right pyelogram was done.

Dr. Colby: At that time I did not know of the pain in the left groin and flank.

Dr. Jacobson: To go back to the case, it is of interest that the duration of the whole illness prior to entry was three or four days after the onset of clinical tetany and oliguria. There is no question that the patient had some type of renal insufficiency with other complications later. This certainly is not an orthodox case of diffuse renal failure. There are many things lacking for a positive diagnosis of terminal chronic glomerulonephritis or chronic vascular nephritis, such as the absence of history of previous acute or chronic vascular renal disease. The patient had normal blood pressure. Many usual symptoms of uremia were absent. It is significant that she had a normal carbon dioxide content of the blood and no clinical or chemical evidence of acidosis. It is also important that she had a normal fixed base, a normal sodium in the blood, which is not an ordinary finding in uremia due to diffuse renal disease.

The first thing that struck me as unusual, regardless of the cause of renal insufficiency, was the presence of marked tetany in association with an extremely low blood calcium and extremely high blood phosphorus. This is a combination that I have never seen in renal insufficiency. It is true that the serum calcium sometimes falls slightly in ordinary renal failure; it may fall to 9.0, 8.5 or 8.0 mg. per 100 cc. I have never seen it fall in renal failure to a tetanic level. The rise of the phosphorus, of course, can be entirely due to phosphorus retention by insufficient kidneys. On the other hand the presence of a positive Sulkowitch test, which means an excess of calcium excretion in the urine, is a stumbling block in trying to explain the whole metabolic set-up. With a mild degree of hypocalcemia, of chronic terminal nephritis, the calcium excretion is either unchanged or is lowered as pointed out by Albright and Bauer[1] many years ago. Could this degree of hypocalcemia be related to the lowering of the serum protein? In cases of renal insufficiency accompanied by mild hypocalcemia, it is thought that the depression is due to or related to the slight depression of serum protein, but in this particular case the lowering to 5.2 gm. does not seem adequate to explain the marked hypocalcemia. I should estimate with this degree of hypoproteinemia that the calcium might otherwise be lowered to approximately 8.5 mg., calculating about 2.0 mg. attached to protein. So far as I can see there is only one known entity in which this type of calcium and phosphorus and clinical tetany can fit properly, and that is hypoparathyroidism. On the other hand, the positive Sulkowitch test is against that diagnosis, because in real hypoparathyroidism, with tetany, the calcium excretion in the urine goes down very markedly. I think the degree of hypocalcemia and the tetany make it likely that this patient had hypoparathyroidism rather than the hypocalcemia of renal failure.

The onset of oliguria suggests that renal insufficiency, with deficiency of renal secretion, had occurred, and it is worth while to consider the various causes of failure of renal secretion. Defective renal secretion is often seen in clinical shock and in conditions of severe dehydration, that is, prerenal failure, when there is not enough blood circulating to the kidneys to secrete urine. There is no evidence of postrenal failure. No lesion in the ureters or pelves that is obstructing the outflow of urine can be demonstrated.

What are the possible intrinsic renal causes of failure of renal secretion? The most frequent cause is some type of tubular obstruction or, in these days, poisoning from the administration of sulfonamides. Poisoning of the tubules with mercury can produce a somewhat similar picture. There is no evidence that the patient had an incompatible transfusion, with the precipitation of hemoglobin in the tubules, or that she had precipitated Bence-Jones protein in the tubules. We are told that so far as could be ascertained the patient had recently taken some stilbestrol, phenobarbital, aspirin, and Karoid with bile salts. So far as I know there is nothing in these drugs to produce tubular obstruction. In view of the fact that she had had some urinary-tract infection over a period of years one wonders whether she had not been given sulfadiazine or sulfathiazole prior to the onset of this illness. We have no evidence of sulfonamide administration in this case.

We must boil down this type of renal failure to something. Could this possibly be the terminal stage of chronic pyelonephritis? There are many

things against and a few things suggestive of this possibility. Against the diagnosis is the fact that this woman had been well, with no long history of symptomatic urinary-tract infection. On the other hand we know that at least nine years previously she had a moderate amount of urinary-tract infection. I suspect that at that time the urinary findings with high specific gravity of 1.026 represented cystitis. There is no evidence of an infectious renal lesion, such as tuberculosis, or, at the time of entry, of generalized sepsis that might have terminated in multiple renal abscesses. Against the diagnosis of chronic pyelonephritis is the normal pyelogram and, possibly, the absence of leukocytosis. For the diagnosis of pyelonephritis, however, we have three points: at least nine years previously she was known to have a urinary-tract infection; for about nine months prior to entry she was said to have some pain in the left flank; and finally, the urinary sediment at the time of admission consisted mainly of white cells and granular casts consistent with the picture of pyelonephritis. We are told that the one small specimen of urine observed was amber in color. That would suggest a specific gravity much higher than that found in secondary renal failure.

This patient undoubtedly died partly because of a complication of the treatment. Most of us have read a fairly recent clinical report in the *Journal of the American Medical Association* by Fine et al.[2] on the removal of nitrogenous bodies in the blood by lavage of the peritoneal cavity, using the peritoneal cavity as a dialyzing membrane. That was obviously attempted in this case. That dialysis did something is evidenced by the fact that the blood nonprotein nitrogen dropped considerably. The patient did not die with the clinical picture of uremia. On the other hand the increasing abdominal distention and tenderness certainly suggest the onset of generalized peritonitis, and later we are told that colon bacilli and nonhemolytic streptococci were grown from the lavage fluid.

She had some type of pulmonary complication terminally, probably bronchopneumonia, and undoubtedly had generalized sepsis terminally. I have mentioned many of the stumbling blocks that I have tried to circumvent, and I am afraid I am forced to forget one thing: the positive Sulkowitch test, which does not agree with anything. It is possible that calcium or milk was administered shortly before the urine was tested for calcium. For want of a better diagnosis I shall rest on the following: idiopathic hypoparathyroidism, pyelonephritis (*Staphylococcus albus*), generalized peritonitis, bronchopneumonia and terminal pericarditis.

DR. MALLORY: Would anyone like to ask any questions of Dr. Jacobson, or does anyone wish to suggest any other diagnosis?

DR. JACOB LERMAN: I recall a patient who had a diffuse pyelonephritis with tetany and another several years back, and I am sure that in Dr. Albright's series we could find several other examples.

DR. BUTLER: I do not see how Dr. Jacobson can entertain the diagnosis of hypoparathyroidism in this case with a nonprotein nitrogen of 136 mg. per 100 cc., going up to 225 mg., unless the patient when she came in was extremely dehydrated and the degree of dehydration overlooked. The statement is made that she was moderately obese, and obesity often obscures dehydration. What evidence have we concerning the degree of dehydration that resulted from this woman's vomiting prior to entry?

DR. CHARLES BURNETT: She was not particularly dehydrated on entry.

DR. JACOBSON: May I ask Dr. Butler if he believes that the degree of abnormality of calcium and phosphorus in the blood is compatible with nothing but renal insufficiency?

DR. BUTLER: I think that is compatible with renal insufficiency. It is not unusual to find a serum calcium of 5.0 mg. per 100 cc. with a serum protein of 5.4 gm., and an inorganic phosphorus of 9.0 mg. in a patient with marked renal insufficiency and elevated nonprotein nitrogen. Unless the patient was severely dehydrated I do not see how the elevation of the serum nonprotein nitrogen could be compatible with hypoparathyroidism.

DR. JACOBSON: I do not believe that such a degree of hypocalcemia in uremia is usual in adults.

DR. BUTLER: I have seen at least six patients on the adult wards of this hospital with this degree of hypocalcemia in uremia. I am still puzzled about the retrograde cystoscopic examination, puzzled in two respects. First, here is a patient who was having frequency rather than polyuria. Until we got the cystoscopic examination we suspected that a patient of this age with frequency and a history of renal infection might have cystitis but the cystoscopic examination was against it.

DR. COLBY: She had no evidence of cystitis from the examination of the bladder.

DR. BUTLER: In the hypocalcemia of hypoparathyroidism one gets bladder retention, not frequency. There was a history of frequency and not of bladder retention, which I think is against the hypocalcemia of hypoparathyroidism.

The second thing in the retrograde pyelogram that bothers me is why, if one subjected the left ureter to the trauma of putting a catheter up, one was too timid to inject a little dye to see what the left pelvis looked like. That was the kidney concerning which there was a history of pain.

DR. COLBY: Perhaps we were timid about this. On the other hand simultaneous injection of dye to both kidneys has been found dangerous. This woman was passing a small trickle of urine, and I suppose we believed that if we did a bilateral pyelogram and the trickle completely stopped we should think that there was a possibility of having caused complete anuria by this procedure.

DR. MALLORY: Dr. Burnett, will you give us the clinicians' impression on the ward about this patient?

DR. BURNETT: After repeated questioning we believed that we had ruled out any toxic substance. There was no history of the taking of mercury. We also considered sulfonamides, and repeated questioning during life gave no leads whatever. Our opinion at the time of death was that we were dealing with a bilateral nephrosis of the kidneys. We simply did not know why she had an acute renal shutdown. Subsequent to death we got an additional history that some time during the winter before admission the patient took 6 or 8 gm. of a sulfonamide, probably sulfadiazine. There was a considerable amount of the drug around the house that the family took from time to time, although there was no definite history that she took it before her illness.

CLINICAL DIAGNOSIS

Acute uremia due to idiopathic renal disease.

DR. JACOBSON'S DIAGNOSES

Idiopathic hypoparathyroidism.
Pyelonephritis (*Staphylococcus albus*).
Generalized peritonitis.
Bronchopneumonia.
Terminal pericarditis.

ANATOMICAL DIAGNOSES

Sulfonamide nephrosis.
General peritonitis.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The autopsy, unfortunately, was limited to the examination of the kidneys. We cannot tell you anything about the parathyroid glands. At autopsy the kidneys looked remarkably normal for a woman who had been totally anuric for two weeks. On cutting frozen sections, however, it became evident that all the lower nephron segments were filled with pigmented casts, that there was interstitial inflammation and that there were crystals in some of the tubules that closely resembled sulfonamide crystals. To check the last point, a portion of one kidney was sent to the Chemistry Laboratory, and the material was identified as sulfadiazine. In spite of the negative history we thus have proof that she had ingested some amount of sulfadiazine. The other ordinary causes of lower-nephron nephrosis are absent in this case. There was no blood transfusion, no history of any state of shock, and no extreme dehydration. We know that sulfonamides can produce this lesion. The logical conclusion is that we consider this sulfonamide nephrosis, presumably due to an abnormal sensitivity of this particular patient to the drug.

DR. JACOBSON: Was there peritonitis?

DR. MALLORY: The immediate cause of death was peritonitis.

DR. JACOBSON: How do you explain the normal carbon dioxide content, Dr. Butler?

DR. BUTLER: I think it can be explained by the fact that she had been vomiting prior to coming to the hospital and had been taking alkalies. Without the vomiting and without the alkalies the anuria would have been accompanied by acidosis. She came in with a low serum chloride and normal carbon dioxide content, because of the coincidental vomiting and ingestion of alkali.

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CASE 32242

PRESENTATION OF CASE

A sixty-year-old man entered the hospital because of difficulty in swallowing.

Two years before admission the patient allegedly vomited about two spoonfuls of bright-red blood. Shortly thereafter he noticed difficulty in swallowing meat, which "got down to the stomach and came right up again." Over a period of a year and a half the difficulty progressed to include all solid foods and then semisolid food until six months before admission, when it became impossible for him to swallow anything but fluids. His diet consisted of ice cream, milk, soup, eggnog, beer and whiskey. The last two items had been a dietary staple for many years, with an estimated daily intake of three or four glasses of whiskey and several glasses of beer. With this illness the patient lost 25 to 35 pounds. He felt weak and hungry, but had no pain or recurrence of hematemesis. The stools had never been black.

Physical examination revealed a thin, pale man, whose skin was hanging in loose folds in many areas. The tongue was coated with caked brown material. The abdomen was soft and flabby. The liver edge extended 5 cm. below the rib margin and was not tender. There were external hemorrhoids. The prostate was small and tender.

The temperature was 98.6°F., the pulse 70, and the respirations 20. The blood pressure was 110 systolic, 75 diastolic.

The red-cell count was 4,030,000, with 12.5 gm. of hemoglobin. The white-cell count was 7800, with 80 per cent neutrophils. The urine had a specific

gravity of 1.014, and the sediment contained 4 white cells and 2 red cells per high-power field. A stool was guaiac negative.

X-ray examination of the esophagus showed an area of constriction at the level of the tenth thoracic vertebra. A hiatus hernia of moderate size was present. The junction between the esophagus and the hernia was markedly constricted, and one area strongly suggested an ulcer crater (Fig. 1). The stomach was normal, but the duodenal cap was deformed. No definite crater was demonstrated. In the chest film the lung fields were bright. The heart was normal in size.

The prothrombin time was 27 seconds (normal, 21 to 25 seconds). The total serum protein was 7.7 gm. per 100 cc., with 5.3 gm. of albumin and 2.4 gm. of globulin. The van den Bergh reaction was normal,

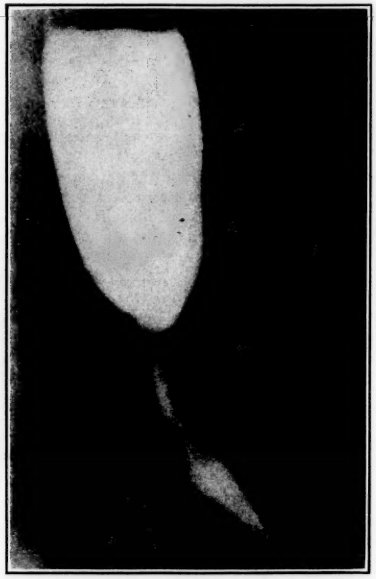

FIGURE 1.

but the cephalin-flocculation test was + at twenty-four hours and +++ at forty-eight hours. The nonprotein nitrogen was 26 mg. per 100 cc.

An operation was performed on the thirteenth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. EDWARD B. BENEDICT: When any man of sixty comes in with difficulty in swallowing, we ought first to consider carcinoma of the esophagus. This patient is within the age group. On the other hand, two years' duration is a little long, although I have seen carcinoma of that duration.

The vomiting of blood goes with carcinoma, benign stricture, esophageal ulcer or esophagitis. Benign stricture is the second thing I should consider in a patient who has difficulty in swallowing.

Patients cannot always tell how far a piece of food goes down, but it is fairly significant if it comes up immediately.

This patient did not have much of a diet; he must have been malnourished. Beer and whiskey may be taken by a patient with either carcinoma or benign stricture, but I must say that excessive use of alcohol may lead to an esophagitis and possibly esophageal ulcer and stricture.

The weight loss does not help. One can lose weight from carcinoma or esophageal obstruction from low intake of food. Pain is more likely in esophagitis and ulcer than in cancer of the esophagus; in cancer, pain appears rather late.

The enlarged liver makes me think of either metastatic cancer or cirrhosis because of the alcoholic history.

Out of 45 cases of benign stricture of the esophagus that I have looked up, 17 were associated with hiatus hernia, 15 with duodenal ulcer, 8 with esophageal ulcer, and 7 with esophagitis without any of these other factors, which may occur singly or multiply. This patient had hiatus hernia, possibly with esophageal ulcer and evidence of old duodenal ulcer, all of which are consistent with a benign stricture. May we see the x-ray films?

DR. JAMES R. LINGLEY: I think that the spot films demonstrate the area in the esophagus best. This is the area of narrowing and the esophagus above this point is dilated. The margin comes down to a small taper rather than a shelf. Below the area of constriction one can see gastric mucosa. Evidently the hiatus hernia extends well up to the area of narrowing. On two of the films there is slight pooling of barium at this point, which is consistent with superficial ulceration, although that is not too definite. This is the deformity of the duodenum; there is gross deformity and constriction at the apex of the cap, without a definite crater.

DR. BENEDICT: You do not see any suggestion of a shelf at that point either?

DR. LINGLEY: No; it is a smooth, tapering shadow.

DR. BENEDICT: All the laboratory findings were within normal limits. The cephalin-flocculation test was + at twenty-four hours, which means very little, and +++ at forty-eight hours, which is not sig-

nificant either. So far as liver damage is concerned, none of the tests indicate whether we are dealing with cirrhosis or metastatic cancer of the liver, if either.

I should hope that the operation performed was an esophagoscopy, which is the first thing to do, not only for positive diagnosis by biopsy but also for treatment by bougienage if a benign stricture is found. The treatment of benign stricture of the esophagus by esophagoscopy and bougienage is unusually satisfactory. I saw a recent case of esophageal obstruction with carcinoma of the esophagus and a large liver, which we thought was metastatic carcinoma of the liver and which proved on peritoneoscopy to be cirrhosis. If this case was carcinoma of the esophagus, which I do not think it was, there could have been metastases to the liver. I believe that it was a benign stricture of the esophagus, and the patient may have had early cirrhosis of the liver. My diagnosis is therefore benign stricture of the esophagus, in association with hiatus hernia, esophageal ulcer and duodenal ulcer, and question of cirrhosis of the liver.

Dr. F. Dennette Adams: Is it not simpler to explain the large liver by malnutrition and the rigid feeling in the abdomen by the fact that the patient was formerly fat and had become extremely thin?

Dr. Rodolfo E. Herrera: As I remember it, Dr. Sweet and I thought that this man had a duodenal ulcer, short esophagus and hiatus-hernia syndrome, so that preoperatively we were quite certain that it was a benign stricture, but because of the question of ulcer of the esophagus and the amount of stenosis, we believed that he probably could be cured more permanently and more quickly if he were operated on than if he had bougienage for a long time. At operation a markedly stenosed short esophagus was found, and as is frequently noted it was difficult to visualize how this condition might have been treated successfully with repeated dilatations alone. The patient had a resection of the lower esophagus and a portion of the cardia and an esophagogastric anastomosis. The patient did extremely well. The postoperative course was uneventful. He was discharged on a six-meal bland diet.

Clinical Diagnosis

Benign stricture of esophagus.

Dr. Benedict's Diagnoses

Benign stricture of esophagus.
Hiatus hernia.
Esophageal ulcer.
Duodenal ulcer.
Cirrhosis of liver?

Anatomical Diagnosis

Benign stricture of esophagus.

Pathological Discussion

Dr. Tracy B. Mallory: The specimen from this patient consisted of 6 cm. of esophagus in addition to a cuff from the cardia of the stomach. At about the mid-portion of the esophageal segment, there was a short constriction 6 mm. in length where the lumen was reduced to a bare 4 mm. in diameter. The mucosa was smooth and not ulcerated at any point. The sections through the area of constriction showed only nonspecific inflammatory reaction and fibrosis, an entirely benign lesion. There was nothing in the section that would give one any indication of the cause of the stricture.

Dr. Richard H. Sweet: Was there any evidence of gastric mucosa?

Dr. Mallory: Not in this case.

Dr. Herrera: I have seen this patient once in the Out-Patient Department. Six months after operation he is back to his old diet, including whiskey and beer, and has told me that he has begun again to have some difficulty in swallowing large pieces of solid food. He was referred to the diet kitchen for a six-meal bland diet, to the X-ray department for further study and to Dr. Benedict for esophagoscopy.

Dr. Sweet might like to comment on the few cases we have seen of gastrointestinal symptoms following resection of the esophagus for inflammatory disease.

Dr. Sweet: As Dr. Benedict has pointed out, a short esophagus with ulcer, inflammatory changes and stricture is frequently associated with a hiatus hernia and a duodenal ulcer. The short esophagus and the hiatus hernia I believe to be congenital. There is a difference of opinion regarding etiology. I can never see how an inflammatory stricture, which is often confined only to a short length up and down the esophagus, can pull the cardia 10 or 12 cm. out of the abdomen into the chest. Some of the cardias are as high as the inferior pulmonary vein. I do not know why we hurdled over the esophagoscopy at this time unless it was that Dr. Benedict was not here. We have had cases in which the hazards of esophagoscopy were considerable, and I might have decided in his absence not to do it. I am not quite prepared to make a definite statement about this, but I have the distinct impression that there is a high incidence of carcinoma in cases of short esophagus. I shall say it this way: a large number of our cases of carcinoma at the lower end of the esophagus have been seen with this anatomical stricture. In one of Dr. McKittrick's patients on whom he asked me to operate, around the corner at the lower end of the gastric side, far beyond the reach of any instrument, there was in addition to this inflammatory stricture a carcinoma as large as a cherry. It is an interesting group of cases. Another point is that I agree with Dr. Bene-

dict that in all these cases bougienage should be attempted if carcinoma can be excluded. We have not always been able to carry out bougienage. I remember one patient who was transferred to the psychiatric ward because when his wife came to visit him his swallowing difficulty was worse. He ended up with carcinoma and, after we had watched him on the wards for a number of months, was completely inoperable. It did not do him any good to be on the psychiatric ward. We must be extremely careful, and I prefer to err on the side of being radical in some of these cases.

As Dr. Herrera mentioned we have had one or two patients who have had recurrence of esophagitis following resection, possibly because we did not resect enough or possibly because of some inherent tendency to develop esophagitis. We have another patient in the Baker Memorial Hospital whose esophagus Dr. Benedict is in the process of dilating following resection of an area of esophagitis with stricture. It is a condition that must be studied and worked on a great deal longer before the best methods of treatment are fully established.

DR. BENJAMIN CASTLEMAN: Do you ever see a peptic ulcer due to regurgitation of acid into the esophagus following resection of the lower esophagus?

DR. SWEET: We have seen one in a patient who had a gastrostomy.

DR. BENEDICT: That is the one I have just treated by esophagoscopy and bougienage.

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ONE HUNDRED AND SIXTY-FIFTH ANNIVERSARY

The one hundred and sixty-fifth anniversary of the Massachusetts Medical Society, held at the Hotel Statler, Boston, was a fitting celebration of the postwar resumption of the more or less normal activities of the Society. The total registration — 1750 — established an all-time high, which is surprising in view of the fact that many fellows, as well as many recent graduates who have postponed joining the Society, are still serving with the armed forces.

The annual meeting of the Council was presided over by the retiring president, Dr. Reginald Fitz, with his customary expertness. There were few controversial matters, and all recommendations by standing and special committees, which at times had been amended by the Executive Committee, were adopted. The report of the Committee on Medical Education, which had been instructed to make a survey of the medical educational facilities available in New England, was of particular interest. Based on a factual study of correlated material from many sources, it was concluded that New England, at the moment, does not need a new medical school and that its present schools can meet the anticipated requirements for the next several years. The increasing activities of the Society were responsible for a request for an extraordinary appropriation to cover the cost of additional secretarial help, which was granted, by the Council. The officers elected for the current year are as follows: president, Dwight O'Hara; president-elect, Edward P. Bagg; vice-president, Isaac S. F. Dodd; secretary, Michael A. Tighe; treasurer, Eliot Hubbard, Jr.; assistant treasurer, Norman A. Welch; and orator, Leland S. McKittrick.

At the annual meeting of the Society, Dr. Fitz gave an excellent talk covering what had transpired during his year of office. After presentation of the incoming president and president-elect, Dr. Frank H. Lahey delivered the annual oration, which will appear in the June 20 issue of the *Journal*.

The annual dinner was attended by approximately 525 fellows and guests. The speakers, Dr. Roger I. Lee and Dr. Elmer S. Bagnall, ably discussed many matters that are of general interest to the medical profession, particularly those having to do with the health of the Nation.

The scientific sessions comprised many well conceived and well presented papers. The Shattuck Lecture was presented by Dr. John B. Youmans, professor of medicine, Vanderbilt University School of Medicine, and formerly colonel, M.C., A.U.S., and chief, Nutrition Branch, Office of the Surgeon General. This paper, entitled, "Nutrition and the War," appears elsewhere in this issue of the *Journal*.

The luncheon meetings of the sections were extremely well attended, as were both the scientific and the technical exhibits, which were excellent. Indeed, many of the exhibitors were enthusiastic over the number of fellows who had visited their booths.

Much of the success of the meeting is due to the diligence and efforts of Dr. Roy J. Heffernan and his committee and of Robert St. B. Boyd, the executive secretary. To them the Society should be duly grateful.

TETANUS PROPHYLAXIS AND TREATMENT

Sufficient time has now elapsed since the termination of the military campaigns to permit a certain amount of stocktaking with respect to the efficacy of some of the procedures used in the medical departments of the armed forces. Brigadier Boyd[1] has now collected and analyzed the cases of tetanus that occurred in the British Army in the African and European theaters of war. His analysis, although based on only 103 cases, brings out many significant features concerning the value and relative importance of active and passive immunization against tetanus.

Boyd points out that the value of the use of prophylactic tetanus antitoxin for passive immunization was adequately demonstrated during World War I. At that time the incidence of clinical tetanus was reduced from a former rate of 8 cases per 1000 wounded to 1 per 1000 among those who received antitoxin within a reasonably short period after sustaining a wound. The average incidence of tetanus among British troops for the years 1914–1918 was 1.47 per 1000 wounded.

In World War II, about 90 per cent of the British troops received prophylactic tetanus toxoid injections. At first, two doses of 1 cc. each were given six weeks apart. In January, 1941, the standard procedure was changed to include a third dose, and in November, 1942, an annual booster dose of 1 cc. of toxoid came into use. Shortly before the invasion of Europe all members of the army groups received a booster dose. Passive immunity by the injection of 3000 units of antitoxin at weekly intervals for three doses after wounding was recommended for those who had not received active immunization, and a single similar dose was suggested for those who had received toxoid injections. In the United States Army only a booster dose of tetanus toxoid was generally used after wounds had been sustained.

The 103 cases of tetanus included 35 battle casualties, an incidence of 0.14 cases per 1000 casualties. The remaining cases comprised 18 non-battle casualties and 50 partisans and prisoners of war. Of the 35 cases among battle casualties, 16 were in men who, for some reason or other, had escaped active immunization. Indeed, considerable evidence was accumulated, pointing to the fact that clinical tetanus was rare among those who had been actively immunized. For example, among the British Expeditionary Force in Europe during 1939–1940, there were 7 cases of tetanus among the 10 per cent of troops who had not been immunized, whereas not a single case occurred among the 90 per cent who had been given toxoid. In another campaign, there were only 6 cases of tetanus among 103,343 wounded British troops, most of whom presumably had been immunized, whereas there were 25 cases among a small number of wounded prisoners taken during that campaign, none of whom had been actively immunized. As compared with 1.47 cases per 1000 in World War I, there were only 0.06 cases per 1000 in this war, a ratio of almost 25:1.

Further analysis of the possible causes of this marked reduction in incidence of tetanus left little room for doubt that only active immunization was responsible. Evidence was obtained that indicated that the low incidence of tetanus among the British Expeditionary Force in Belgium was not due to any peculiarity in the type of terrain in which the wounds were incurred. Thus, data unearthed in a captured German hospital in Brussels showed that there had been 100 cases of tetanus among unimmunized troops who were wounded in the same terrain in which no cases occurred among the British Expeditionary Forces. Prophylactic treatment with sulfa drugs and penicillin was likewise ruled out as a significant factor.

Several points concerning the effect of active immunization on the severity of the disease and on mortality were also brought out quite clearly from Boyd's study. In the first place, the crude mortality in all the clinical cases during this war was 46.6 per cent, which is practically the same as that observed in 1914–1918, when it was 50 per cent. The mortality was inversely proportional to the length of the incubation period, which reflects a

direct relation to the severity of infection. The case mortality among those who were protected by active immunization was almost identical with that among the unprotected. It is of interest to note, however, that there were no deaths among persons who had received two or more booster doses of toxoid.

Most important, however, was the bearing of previous active immunization with toxoid on the efficacy of passive immunity conferred by the prophylactic injection of antitoxin. Among those who had been actively immunized with toxoid there were 2 deaths in 11 cases (18 per cent) in which prophylactic antitoxin had been given, as compared with 9 deaths in 11 cases (82 per cent) in which such passive immunity had not been used. Among those not actively immunized, there were 10 deaths among 23 patients (44 per cent) who had received prophylactic tetanus antitoxin, and 19 deaths among 39 patients (49 per cent) who had not received antitoxin. In other words, passive protection with antitoxin administered soon after wounding did the most good in the persons who had previously been actively immunized with toxoid.

Pratt,[2] in reviewing the experiences with tetanus at the Children's Hospital in Boston noted that the severity of the disease was the most helpful factor in determining the outcome. As already noted, severity is inversely proportional to the length of the incubation period. In Boyd's study the incubation period in the actively immunized patients was significantly lower than that in those who had not been protected by toxoid. In the protected patients symptoms began in most cases before the tenth day, whereas in most of those who had not been actively immunized with toxoid the incubation period was more than ten days. This appears to indicate that it was necessary to have a much severer disease, in which toxin production occurred at a rapid rate, to break through the residual antibody resulting from the previous toxoid immunization. This breakthrough, moreover, had to take place before the stimulus to renewed antibody production had become effective enough to raise the antitoxin level to a protective value.

The number of cases in Boyd's study was inadequate for an analysis of the value of various therapeutic measures. Early and intensive treatment with antitoxin seemed to be quite valuable. This was suggested by the fact that there were 7 deaths among 18 patients (39 per cent) who received 100,000 or more units within the first thirty-six hours of symptoms, as compared with 14 deaths among 20 patients (70 per cent) not so treated. No additional benefit could be definitely ascribed to penicillin, but this was difficult to assess in the few cases in which it had been used. The same is true in the cases in civilians recently reported by several authors.[3–5]

Boyd concluded that tetanus was not entirely prevented by active immunization, since there were 22 cases among actively immunized persons in his series. Furthermore, the case mortality in actively immunized individuals was not below the average, but he points out that most of the fatal cases occurred among colored troops. The mortality, however, was significantly lower in actively immunized persons who received prophylactic antitoxin. Also the duration of symptoms in actively immunized patients who survived was significantly lowered. Failures of active immunization were attributed to inadequate levels of antitoxin remaining in the blood at the time when the infection took place, and he believes that the best way to remedy this is by the use of prophylactic antitoxin rather than by giving a booster dose of toxoid, as recommended in the United States Army. To be effective in therapy, antitoxin must be given as early as possible, in large doses and intravenously. The experiences of the United States forces have not yet been reported, but there is reason to believe that they were at least as favorable as those of the British in spite of the fact that the use of antitoxin was not encouraged.

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MASSACHUSETTS MEDICAL SOCIETY

DEATH

ALLEY — Ernest J. Alley, M.D., of Billerica, died May 23. He was in his seventy-second year.

Dr. Alley received his degree from the University of Vermont College of Medicine in 1899.

His widow and two daughters survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

PSITTACOSIS

Recently a case of psittacosis was reported from the North Metropolitan Health District. Subsequent investigation of the possible sources of this disease led to birds and bird dealers in various sections of the Commonwealth. Inasmuch as the clinical appearance of psittacosis cannot readily be distinguished from that of so-called "virus pneumonia" (of which it is actually one form), there may be more psittacosis in Massachusetts than one suspects.

Birds in the possession of dealers and in private homes, which die of "unknown causes," or diarrhea or any disease characterized by coughing, should be packed in dry ice and sent by air mail to the National Institute of Health, Bethesda, Maryland, for study, with psittacosis in mind.

Samples of serum taken under aseptic precautions from patients who have been in contact with birds and who develop atypical or virus pneumonia should be sent to Dr. Karl F. Meyer, Hooper Foundation, San Francisco, California, for the psittacosis complement-fixation test.

CORRESPONDENCE

QUALITY OF MEDICAL CARE

To the Editor: In the April 25 issue of the *Journal* you print an excellent editorial concerning the quality of medical care. You say, in part: " . . . many thousands of graduates of substandard schools are in active practice. Undoubtedly some of these physicians give better medical care than do certain graduates of approved schools. . . . Mere graduation from an approved medical school is no guarantee of an efficient and up-to-date practitioner." You are more than right on both these counts. Many young men go in for medicine because they are forced to by their parents and not because they have any real call to practice medicine. Medicine not being their vocation, they amble through life making weak medical gestures. Some rich persons wish to have a doctor in the family and are willing to pay for the luxury, but the doctor does not amount to much because he does not have the soul of a practitioner. One requires a soul, courage and much more if he essays to succeed in a rural New England practice. Some graduates become so-called "institutional men"; they take salaried hospital jobs, knowing that they would go down swiftly out in the competitive field. Such men would simply dry up and blow away if they did not have a job or private means. They are in no sense practitioners.

Graduation from an unaccredited medical college in no way implies inferiority. It is well known that many of the graduates of the so-called "substandard" medical schools can leave many of their brethren far behind on all counts. It has been said that the top 20 per cent of the poorest medical school are better informed than the lowest 20 per cent of the best medical school. I believe that this statement is unfair to the unaccredited medical schools and that their graduates rank higher. If graduation from small unaccredited medical schools implied inferiority, the world would never have heard of a lot of men whose names are outstanding in the history of medicine and surgery.

In your editorial you speak of a plan in Massachusetts whereby doctors will be admitted to certain privileges in hospitals, such as making rounds, attending clinics and doing other things to improve their education and abilities. This is sound, and I hope that it will come to pass, but as you say yourself some doctors will probably "scorn" to avail themselves of the hospital invitation. Since the American College of Surgeons has definitely taken the ball away from other big medical associations and has imposed its imperious will on hospitals and countless doctors, the word "scorn" is the correct term. The College has imposed a sort of serfdom on the general run of the profession, something like the *osculum infame* of the ancient European guilds. It will be interesting to see how far they will get with it these days. They have done quite a lot so far, and all in name of "higher standards," "accrediting" or what have you. These terms are a few of the bludgeons held over the hapless heads of many institutions. This has been going on for years, and aside from exterminating a lot of their own brethren, it does not appear that they have accomplished a thing that could not have been done much better in another way. The net result seems to have been the scourging of a lot of hapless physicians and small colleges and hospitals.

The irregulars have increased immensely; indeed thousands of fine medical recruits have been driven into the ranks of the irregulars, where they practice about everything the regular doctor does and prosper apace. The witch hunt, which is still going on, has not bothered the irregular doctor, in fact it has been a boon to him. He has found out that laboratory work, physiotherapy, x-ray technics, minor surgery, sclerosing therapy, medical and surgical diathermy all lend themselves beautifully to office practice. If a case of serious illness comes up, a hospital contact is not difficult to make.

Your editorial states, "Recently graduated physicians shun small cities and rural communities." You bet they do. Why not? Why should a graduate from high school, college, medical school and hospital, with perhaps another stretch of postgraduate training, bury himself in the woods and snow drifts? He is a fool if he does. Our standards are not too low: they are too high, and there is too much stress on specialization. In this vicinity there are towns that had from two to four doctors from Revolutionary days up until a few years ago. Not now, your recent graduate fades gracefully. The big medical associations in their craze to raise standards have exterminated the sturdy, capable, general practitioner who formerly rode these hills.

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NOTICES

HARVARD MEDICAL ALUMNI ASSOCIATION

The annual meeting and dinner of the Harvard Medical Alumni Association will be held at the Sir Francis Drake Hotel, San Francisco, on July 3, during the period when the annual meeting of the American Medical Association is in session.

SOUTH END MEDICAL CLUB

The next regular meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, June 18, at twelve noon. Dr. Samuel Proger will speak on the topic "Water Imbalance."

Physicians are cordially invited to attend.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JUNE 20

FRIDAY, JUNE 21

*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

TUESDAY, JUNE 25

12:00 m.–1:00 p.m. Dermatological Service, Grand Rounds. Amphitheater, Dowling Building, Boston City Hospital.

*12:15 m.–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

WEDNESDAY JUNE 26

*10:30–11:30 a. m. Medical Clinic, Isolation Building Amphitheatre Children's Hospital.

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